Patient Assessment in Clinical Pharmacy

A Comprehensive Guide

Sherif Hanafy Mahmoud
Editor

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For my wonderful wife, Sally, who is always supportive of my crazy endeavors
For my precious kids, Basant, Omar, and Ali, for being the pearls of my life
For every pharmacist, who strives to make life better for their patients

Foreword

The educational training and the role of pharmacists as medication expert healthcare professionals for patient-centered care in the twenty-first century require comprehensive patient assessment. One of the most important skill sets a pharmacist will use in clinical practice is patient assessment. An important aspect of pharmacy practice is effective communication and taking both clinical and scientific information and translating that for patients. Pharmacists work both independently and in teams, and they are professionals who effectively communicate and have a passion for enquiry and seek to understand patients holistically. Canadian pharmacists are some of the greatest luminaries and innovators in the pharmacy profession, and the practice of pharmacy in Alberta has often led the way.

Patient Assessment in Clinical Pharmacy: A Comprehensive Guide is divided into four parts:

Part I. The three introductory chapters provide a foundation of the patient care process and set forth the principles of patient and physical assessment to be followed.

Part II. Symptoms assessment is divided into eight succinct chapters of mental and physical features that may indicate a disease or condition and particular features that are often apparent in assessment of patients by pharmacist clinicians. As pharmacists routinely diagnose and treat common illnesses and refer their patients when required, the highlighted symptomology in this guide can be a sign of an undesirable manifestation, adverse effects, or existence of disease in a patient requiring further follow-up.

Part III. Chronic illness assessment is discussed in a series of ten chapters reflecting some of the major diseases that are often managed by pharmacists independently and in teams involving various body systems including endocrine, cardiovascular, pulmonary, neurology, and musculoskeletal. The pharmacist's role in chronic disease management and self-care is of paramount importance to optimal health outcomes.

Part IV. Specialized assessments are a clinical cornerstone of pharmacy practice, and this section reflects nine areas involving laboratory testing and clinical practice beginning with pharmacokinetic assessment of drug disposition for drug monitoring, extending to laboratory value and biomarker assessment of major organ systems as well as chemical pathology, hematology, blood gases and coagulation, microbiology and immunology,

and an overall understanding and interpretation of clinical biochemistry and assorted diagnostics.

Overall, this guidebook is a reference for pharmacist practice designed for and by pharmacists to augment existing knowledge and skills and to optimize practice and is a welcomed addition to a paucity of focused literature on this subject. This textbook is intended to fill the significant educational apertures in patient assessment that are contemporarily required by pharmacists and educators to provide primary care patient-centered pharmacy services. This textbook further reflects current Canadian pharmacy practice guidelines where applicable and extends them where necessary and prudent. This is a seminal Canadian-authored reference patient assessment book that is intended for a global audience. The potential of this guide to be adopted by pharmacy schools and pharmacists as well as other healthcare professionals is indicative of its quality and the caliber of the pharmacy practitioners and academics in Alberta and throughout Canada and their erudite insights into medication expertise for patient-centered care.

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Preface

Pharmacists' role as healthcare practitioners is evolving as they are taking a more active part in primary patient care. Clinical services are now becoming the forefront of pharmacy practice as pharmacists are helping patients manage their medications and diseases, providing patient education and, in some jurisdictions, prescribing and adapting medications. As medication experts, pharmacists' interventions in patients' care have been shown to improve patient outcomes and reduce healthcare costs in various practice settings. In order to perform their day-to-day duties, pharmacists need a framework to guide care for their patients. This framework is called the patient care process, and it involves three main steps: patient assessment, care plan development, and implementation and monitoring and follow-up. An essential part of the patient care process in addressing patient concerns is complete patient assessment. Patient assessment skills apply to all pharmacy practice settings, including community, hospital, and specialized pharmacy practice. The importance of patient assessment skills together with the scarcity of resources in this topic initiated the idea of this book. The aim of this book is to provide a comprehensive discussion of patient assessment for clinical pharmacists. It is organized into four parts. Part I includes introductory chapters regarding the basics of patient assessment and components of the patient care process. Part II includes a detailed assessment of common symptoms encountered by pharmacists in their practice. Part III discusses assessment of patients with various chronic illnesses. This is followed by Part IV, which addresses select specialized topics and assessment considerations of interest to pharmacists such as pharmacokinetic assessment, critical illness assessment, and assessment considerations in older adults and pediatric patients. This book targets all pharmacists, regardless of their practice setting, and pharmacy students, serving as a valuable tool and resource in their daily practice.

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Part I

Introduction

1 Introduction to the Patient Care Process

Theresa L. Charrois

Chapter Objectives

1. Define and understand the role of the patient care process in providing care.
2. Describe the components of comprehensive patient history taking.
3. Apply a process to patient assessment that can be used in a variety of different patient care settings.
4. Apply a process to assess a patient for drug-related problems.
5. Outline the components of patients' comprehensive care plans.
6. Develop appropriate documentation of patient care.

Background

Pharmacists play an important role in patient-centered care. Being the most accessible of the healthcare team members, pharmacists' role as healthcare practitioners is evolving as pharmacists are taking an active part in primary patient care. With the continuously expanding pharmacists' scope of practice, there is a need for a framework for pharmacists to provide a consistent patient-centered care. Research has shown that pharmacists who are directly involved in the care of patients improve the health outcomes of patients; therefore, it is important for pharmacists to have a fundamental process to provide patient-centered care [1–4].

The patient care process provides such framework and is central to our identity as pharmacists. It is what defines our role as professionals. It includes our scientific knowledge of medications, our clinical knowledge, and our interaction with the patient. The patient care process is a continuous and dynamic mechanism to provide patient care (Fig. 1.1) and includes the essential components that can be adapted to suit various practice settings:

Step 1: Patient assessment
Step 2: Care plan development and implementation
Step 3: Monitoring and follow-up

Assessment of the patient (including a complete history and understanding of why they are seeking care) and assessment of current medications are vital to ensure appropriate care is being provided to the patient (Step 1). Developing a care plan including all drug-related problems, along with goals and implementation of recommendations, is the next step of the process (Step 2). Finally, appropriate monitoring and follow-up helps to ensure goals are being met and that safety is being monitored (Step 3). This framework is

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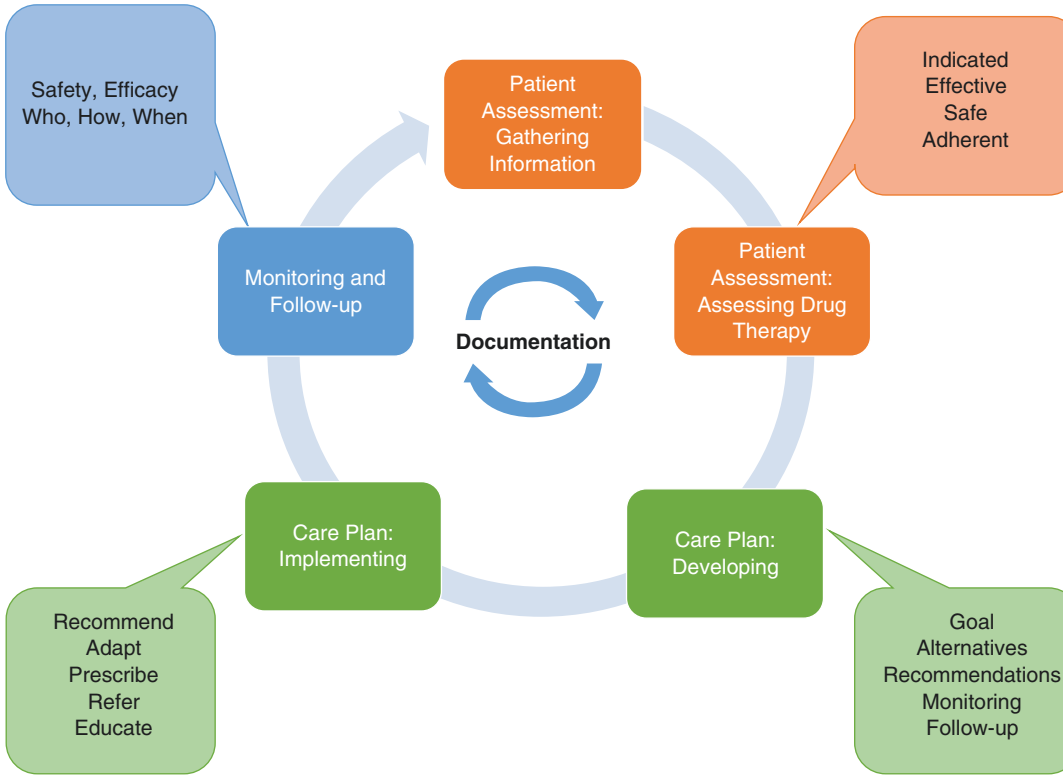


Fig. 1.1 Patient care process

consistent for complete pharmacist assessments of a patient, as well as for targeted assessments, that may be specific to a medical condition. Patient care is then documented to ensure that it is communicated to all other members of the healthcare team.

Assessment

The key purpose of an assessment in pharmacy practice is to determine if a patient's drug therapy needs are being met [5]. Assessment can occur during various types of encounters; for example, at prescription drop off, during routine refill pickup, or during over-the-counter medication (OTC) counseling. Often, pharmacists think assessment can only happen in a private room during a thorough patient interview; however, it should be occurring at any stage of the medication use process. The specific elements of the patient assessment will change based on the situation, i.e., an assessment at refill will differ from an assessment with a new prescription, but the same overall process can be applied regardless of scenario or setting. Within the patient care process there are two primary components of assessment: (1) assessment of the patient, including the patient interview, and (2) assessment of current drug therapy to determine if there are any drug-related problems.

Assessment of the Patient: The Patient Interview and History Taking

Prior to conducting the interview, the pharmacist should establish a relationship with the patient to ensure trust-building and that the patient's goals are clearly defined. This is followed by the structured patient interview. In order to assess a patient, the pharmacist will need to collect

relevant information through multiple sources such as the patient interview, electronic medical records (EMR) (prescription records, lab values, diagnostic tests, etc.), and physical examination. Complete and relevant patient history taking is essential for proper patient assessment. By collating this information, the pharmacist can develop a patient database suited for their particular setting. The information collected and inputted into the database can then be used to assess the patient and develop a care plan.

As part of the patient interview, the pharmacist needs to determine the following: (1) the patient's reason for seeking care, (2) their current symptoms (if presenting with a specific complaint), (3) medical history, and (4) medication history.

In determining the patient's reason for seeking care, it is imperative that the patient's perspective is considered. The patient's goals need to be the priority and can be negotiated with the pharmacist's goals as a care provider. By incorporating the patient's goals into pharmacists' assessment, they can create a sense of trust and shared values for moving forward in a treatment plan.

Symptom assessment can be done in a variety of ways but the key pieces of information that need to be collected remain the same: the region/location, what helps or worsens the symptom, the severity, and the temporality of symptom onset. By using appropriate questions to get at each of these elements, the pharmacist can have a better and more complete understanding of the patient's primary symptom concern. Readers are referred to Chap. 2 for an in-depth discussion on symptom assessment.

A complete and thorough medical history including current and ongoing medical issues, resolved medical issues, and surgical history is a vital part of the process. In certain cases, a pharmacist may need to use physical assessment skills (Chap. 3) to evaluate current conditions, symptoms, and even safety and efficacy of their medications. Whether or not physical assessment is required as part of the patient assessment is dependent on the presenting complaint, reason for seeking care, and the setting where care is being provided.

Clearly, a complete medication history is our true domain as pharmacists, but pharmacists have to ensure they capture the many facets of medications use. Specifically, the medication history needs to include current and past medications, allergies, adverse reactions, immunizations, and patient adherence. Often, patients do not consider natural health products or over-the-counter medications as part of their medication list, and those products should be specifically interrogated. Other factors that may affect drug therapy should also be considered, such as social history (tobacco, alcohol, and recreational drug use) and relevant dietary information. Information such as social history may not always be relevant; therefore, some judgment needs to take place before asking relevant questions. In addition, these questions should be asked in a nonjudgmental way, to again ensure the development of trust between the patient and the pharmacist [6].

At the end of the interview, the pharmacist should be able to determine what is going on with a patient (in terms of presenting complaint and symptoms) and the patient's primary concerns. From this point, the pharmacist can specifically assess the patient's medications. Table 1.1 provides a summary of the elements of comprehensive patient history.

Assessing Drug Therapy

After patient information is collected, the pharmacist must then determine if the patient's current drug therapy is appropriate. The four primary questions a pharmacist should consider for each medication are the following:

Is this medication indicated?
Is this medication effective?
Is this medication safe?
Is the patient being adherent to this medication?

These can be remembered using the acronym IESA: indicated, effective, safe, and adherent. In addition, the pharmacist should consider if there are medical conditions that are not currently treated but may require drug therapy, as a lack of

Table 1.1 Summary of the elements of comprehensive patient history

Elements of a Patient History	Details
History of present illness (HPI)	Assessment of presenting symptoms/complaint SCHOLAR (see Chap. 2)
Medical History; Past medical history (PMH)	Current and previous medical conditions Hospitalizations, surgeries
Medication History	Current medications – indication, dosage, duration (link to current medical conditions), adherence Previous medications Nonprescription medications – including complementary and alternative medications, vitamins, minerals, over-the-counter medications Immunizations
Allergies	Include reaction (date, onset, symptoms, management)
Social History (SH)	Lifestyle considerations – diet, exercise, living conditions Substance use – caffeine, alcohol, tobacco, recreational drug use
Family History (FH)	First degree relatives Focus on conditions with familial linkages such as cardiovascular disease, diabetes, cancer etc.
Laboratory	Complete blood count, electrolytes, renal function (including calculated CrCl), liver function, microbiology, etc.
Review of Systems (ROS)	Head to toe assessment Integumentary, head/neuro, eyes/ears/nose, neck, chest/lungs, cardiovascular, gastrointestinal, urinary, hepatic, renal, reproductive, musculoskeletal, endocrine

drug therapy for a condition is also a drug-related problem. When assessing indication, there should be a clear reason why a patient is on each medication. In addition, you should determine if the medication they are on for a condition is the most optimal therapy – based on the relevant guidelines for practice, comorbidities, and outcomes.

For effectiveness, it makes the most sense to determine what the important patient outcomes and clinical outcomes are for a condition, and if these are being met. This relates back to optimizing therapy. Considerations such as dose increases or additional therapy being added should be taken into account if drug therapy is not effective.

In terms of assessing safety, the main issue we should consider are the adverse effects from the medications. This includes a general overview of common adverse effects of a drug, as well as those rare adverse effects that could be harmful. Asking the patient the question "Are you having any side effects?" is not always helpful, because patients may not link symptoms to drugs. Questions should be tailored to the specific drug. In addition, medication safety can be assessed by reviewing appropriate lab work that was collected during the patient assessment. Drug interactions are also part of a complete assessment of safety parameters; this includes determining if the drug interaction is potentially relevant to this patient and the possible severity of the interaction if the interacting medications are continued.

Medication history also includes an assessment of adherence. When assessing drug adherence, pharmacists should ask the patient in a relevant time period, how often they forget their medications; i.e., *how many pills have you missed in the last week?* This is a relatively nonjudgmental approach to assessing adherence, and judgment when asking about adherence could lead to false answers. When a patient expresses that they are sometimes nonadherent, the pharmacist needs to assess what factors may be leading to this nonadherence in order to help develop strategies to overcome it, such as education, or reminder systems. Nonadherence can be due to multiple factors and can be purposeful or unintended. An assessment of the root cause of the nonadherence will help in decision-making about possible ways to improve it. Adherence may also be medication specific, so assessing adherence globally may not always provide an accurate

Table 1.2 Example of assessing drug therapy appropriateness

Medical Conditions	Medications	Other Information
Hypertension	Hydrochlorothiazide 25 mg daily	CrCl = 75 mL/min BP 126/72 No reports of dizziness, falls Misses dose once/month *(information can be used to assess efficacy and safety)*
Seasonal allergies	*(not currently treated – potential DRP)*	Only in spring
(no current indication – potential DRP)	Omeprazole	Previously had *H. pylori* (1 year ago) No current symptoms of reflux

depiction of actual medication use; questions may need to be targeted to the individual drugs. Both adherence information and assessing drug safety may actually be uncovered during the initial patient interview. Further details regarding adherence are discussed in Chap. 2.

After working through the four medication assessment questions (indicated, effective, safe, adherent), the easiest way of approaching the next step of drug therapy assessment is to link medical conditions to medications. An example is shown in Table 1.2. By linking medical conditions to medications, pharmacists can identify if all conditions are being adequately treated or if all medications have a relevant indication. In addition, monitoring information can be included to assess efficacy and safety. This is a good first step in assessing the appropriateness of a person's drug therapy.

In Table 1.2, the IESA questions are depicted to provide an example of application to a patient scenario. In this example, you can determine that hydrochlorothiazide is indicated for the patient's hypertension and the effectiveness of the hydrochlorothiazide therapy from assessing the blood pressure (BP). Safety may need to be further explored through other questioning on adverse effects, such as dizziness. Adherence is also indicated in the assessment. It is clear from this basic format, that there are no drugs currently being used for seasonal allergies, but perhaps through your initial patient assessment you determined it was unnecessary as the patient preferred to take nothing. In addition, you may determine their may be no indication for the omeprazole, and that may need reassessment.

From this assessment of indicated, effective, safe, and adherence, you can develop a list of potential and actual drug-related problems. It is the identification of these drug-related problems that leads the pharmacist into the next step of the patient care process, which is developing a care plan.

Care Plans

The purpose of a care plan is for a pharmacist to document their assessment of a patient, along with a plan for resolving and monitoring medical conditions and medications. A care plan can take many forms and a variety of templates are available to assist in this process. Table 1.3 provides one example for a template of a care plan. A care plan should not be kept separate from other patient care records, as it is a documented plan for care that other pharmacists on the team, or other health-care professionals in the pharmacist's setting may want to refer to as well.

The primary aspects that should be included in the care plan, after the patient's database is created, are the drug-related problems which were assessed, and for each problem: *goals, alternatives, and recommendations*. *Goals* are meant to be specific to a patient and not just broad and overarching. For example, when considering goals of therapy for blood pressure treatment, you would want to include a specific target blood pressure based on the patient's comorbidities and on current guidelines but also consider any parameters specific to that patient, such as minimizing postural hypotension in a patient who is already concerned about falling. The patient should be asked what their goal is with therapy to help construct goals that make sense to their

Table 1.3 Example care plan template

MEDICAL CONDITIONS & MED-RELATED NEEDS: List and prioritize each medical condition first, followed by any DRPs identified for a given condition. Although some medical conditions may not have a DRP, a care plan is still necessary for ongoing patient monitoring.
GOALS OF THERAPY: For each medical condition and/or DRP state desired goals of therapy/timeframe. **Goals**: cure, prevent, slow/stop progression, reduce/eliminate symptoms, normalize a lab value. *Consider realistic goals determined through patient discussion. Goals of therapy are measurable or observable parameters that are used to evaluate the efficacy and safety of therapy.*
ALTERNATIVES: Compare relevant drug and nondrug therapies that will produce desired goals. List the *pros* and *cons* of each therapy as well as rationale for each being included. *Consider: Indication ● Efficacy ● Safety ● Adherence ● Cost/coverage*
RECOMMENDATIONS/ PLAN: In collaboration with the patient and other healthcare providers, select the best alternative and implement the plan. Provide a rationale for the chosen plan relative to the other alternatives considered. *Consider: Drugs: correct drug, formulation, route, dose, frequency, schedule, duration, medication management. Nondrug: nondrug measures, education, patient referral.*

lifestyle. Not all care plans require *alternatives* for management; however, it is a clear way to follow someone's thought process as to why a particular medication was chosen. By listing relevant and appropriate alternatives, as well as consideration of the pros and cons of each, a pharmacist can be transparent with their decision-making process of determining optimal therapy. From this list of alternatives, *a recommendation* should then be determined. This may mean a need for drug therapy, additional drug therapy, or stopping drug therapy. Lifestyle parameters, such as diet and exercise, can be included in this section as well. Education needs for the patient regarding medical conditions and medications should also be addressed. The recommendations should be succinct but clear, with a plan for who is taking care of each part of the plan.

Monitoring and Follow-Up

Monitoring plans should be developed for each and every drug-related problem. Depending on the situation, you may want to develop a monitoring plan that encompasses all the included drug therapy problems and recommendations, as there could be overlap. For example, in a combined monitoring plan, you could include all required follow-up lab testing in one place. This helps ensure consistency in follow-up parameters, and not sending the patient at multiple time points for blood tests, or for multiple visits to care providers.

For monitoring, specific parameters for both efficacy and safety should be indicated. Efficacy parameters relate directly to the goals of therapy, and the outcomes that are targeted. Safety parameters generally relate to side effects of the medications. Parameters, both for efficacy and safety, can include signs and symptoms, as well as laboratory parameters.

In addition, it is important to indicate who is responsible for the appropriate follow-up. In jurisdictions where pharmacists can order lab tests, the pharmacist can be the person to follow-up on lab results, but that may not always be the case. In addition to noting the respective person responsible for follow-up, a timeframe for when each parameter is monitored needs to be determined. Follow-up visits with patients can be used for a variety of reasons: assessment of meeting goals and outcomes, effectiveness of drug therapy, safety of drug therapy, and also the assessment of any new drug-related problems (using the parameters of indicated, effective, safe, and adherent). Therefore, follow-up visits should be considered a vital component in the care provision of patients.

Table 1.4 Example monitoring and follow-up plan

Medical condition	Parameter	Frequency	Rationale
Hypertension (treated by ramipril 5 mg po BID)	Efficacy: BP <120/80	Daily (by patient – home BP monitor); every 3 months (by family doctor); at refills (by pharmacist)	Target based on patient's comorbidities
	Safety: potassium, SCr, cough	1 week after initiation of ramipril; prn afterwards	
Diabetes (treated by metformin 750 mg po BID)	Efficacy: A1c <7%	q3 months (by pharmacist)	Target hemoglobin A1C as per guidelines
	Fasting blood glucose pre-meals 4–7 mmol/L post-prandial blood glucose 5–8 mmol/L	3× per week (by patient)	
	Safety: GI disturbances such as diarrhea	At refills (by pharmacist)	

BID twice daily, *BP* blood pressure, *GI* gastrointestinal, *prn* when needed, *SCr* serum creatinine

An example of a complete monitoring and follow-up plan is included in Table 1.4. This example is a monitoring plan developed based on the patient's medical conditions.

Documentation

A care plan is meant to be used as a tool specifically for pharmacists, whereas documentation is meant to be a legal document of care provided to a patient and to inform other healthcare providers what care you provided to the patient. Usually, a care plan is significantly longer and more thorough, whereas a documentation note is shorter and more succinct. Documentation is essential owing the following reasons:

- To help maintaining patient safety
- To comply with legal requirements
- To avoid duplication of work
- To facilitate communication
- To comply with standard of practice in different jurisdictions
- To facilitate quality assurance

Documentation can take many forms, such as a quick note in dispensing software, or a longer consult letter that is related to only one particular concern. Notes can be structured (such as DAP, SOAP) or unstructured such as those focused on a complete medication history or only on one specific problem (e.g., assessment of drug levels). Only care that has been documented can be assumed to have been provided: if you did not document the care, it did not happen [5]. A practitioner's documentation will be highly dependent on where they practice, requirements for that place of practice, and how care is communicated between practitioners.

Structured Documentation

By using a structured format to help guide documentation, a pharmacist can ensure the essential information is included. Two common formats are used in practice: the DAP note and the SOAP note. A DAP note includes data, assessment, and plan. Other types of structured documentation can include preprinted forms often used in care facilities and hospitals such as medication reconciliation or allergy assessment forms.

The difference between a DAP note and a SOAP note is that in a SOAP note, the data is further separated into subjective and objective data. Data includes a succinct summary of the information collected in the patient interview that is relevant to the problem being discussed. Only data that relates to the patient assessment that was completed should be included; including too much data that is not directly related to the purpose of the note can make the DAP note unreasonably long. Long notes run the risk of not being read by other members of the care team. Other elements to

include in the data section are the patient's goals and preferences.

The assessment component of the note is the pharmacists' assessment and determination of what the drug-related issue is and the rationale behind the assessment. This includes the pharmacists' professional interpretation of the data presented. The rationale should be clear so that other health-care providers can understand the assessment and consequently, the plan.

The plan includes specific recommendations for the problem, as well as follow-up and monitoring. Recommendations or prescribing decisions should include specifics of dose, route, and duration. Recommendations can also include nonmedication focused interventions such as lifestyle factors. Follow-up should include who is doing what elements of follow-up, so work is not being duplicated. In addition, it should include the timeframe for monitoring and follow-up. Two examples of DAP notes are provided in Boxes 1.1 and 1.2.

Box 1.1 Structured Documentation Example 1: Community Pharmacy

August 1, 2018 9:30 am: Rx#1234567 New prescription for hypertension

Data:
- Mr. Y received a new prescription for hydrochlorothiazide 25 mg daily
- Average BP over last 3 pharmacy visits: 150/82 (May 2018); 153/79 (June 2018); 157/90 (July 2018)
- SCr 85 μmol/L, calculated CrCl 95 m/min, K+ 4.2 mmol/L (labs done yesterday)
- No other medications or medical conditions
- Patient expresses concern about started a regular medication

Assessment:
- Hydrochlorothiazide is indicated as first-line treatment for hypertension and dose appears appropriate. Target for patient is BP <140/90.

Plan:
- Pharmacist to check SCr, K+ in 1 week
- Pharmacist to assess for safety in 1 month at next refill – dizziness, postural hypotension
- Pharmacist to assess for efficacy at next refill: BP measurement in pharmacy
- Pharmacist counseled patient on how to take medication and common adverse effects; discussed patient's concerns about starting medication and offered suggestions to ensure adherence
- Patient to monitor BP at home daily for first week, then a few times a week until next refill. Pt will call pharmacist if any concerns.

Abbreviations: Rx#, prescription number; BP, blood pressure; SCr, serum creatinine; K+, potassium

Box 1.2 Structured Documentation Example 2: Hospitalized Patient

Pharmacist's note RE: Vancomycin

D: 47 F (70 kg, 176 cm) admitted to the hospital for traumatic brain injury 6 days ago. She was started on vancomycin 3 days ago for MRSA hospital acquired pneumonia.

Vitals (today): T_{max} 37.2 (was 38.7); BP 138/75; HR 75; RR 13; O2 sat 95% currently on room air (was on 4L O2 3 days ago)

Labs: SCr 75 μmol/L (stable); est. CrCl ~ 87 ml/min; BUN 7 mmol/L; WBC 9←13←19 × 10^9/L; Neut. 6←10←14 × 10^9/L

Microbiology: Sputum culture (4 days ago): 3+ MRSA sensitive to vancomycin

Chest X-ray (3 days ago): LLL pneumonia
Current antibiotics: Vancomycin 1 g iv q8h started 3 days ago (dose times 00:30, 08:30, 16:30)
Vancomycin level drawn today at 00:02 was 17 mg/L (pre sixth dose)
A: Patient is appropriately treated with vancomycin given the MRSA pneumonia. Vancomycin level was drawn appropriately pre sixth dose and was within target for MRSA pneumonia (15–20 mg/L) and most likely reflects steady state given patient's weight and renal function. The patient is clinically improving (afebrile with less oxygen requirements; improving WBC and neut.)
P: Continue vancomycin at the current dose 1 g iv q8h for a total of 14 days. Team to monitor SCr and CBC at least 2× per week as long as patient on vancomycin. Pharmacist to follow up and order vancomycin levels as appropriate.

Abbreviations: A, assessment; BP, blood pressure; BUN, blood urea nitrogen; D, data; F, female HR, heart rate; P, plan; LLL, left lower lobe; MRSA, methicillin-resistant *Staphylococcus aure*us; RR, respiratory rate; SCr, serum creatinine; T_{max}, maximum temperature in 24 h; WBC, white blood cells count

Unstructured Documentation

There are situations where a full DAP note is not required, such as a note to clarify a previous order, a follow-up note, allergy assessment, renal dosage adjustment, etc. A pharmacist should use their professional judgment about when an unstructured note is appropriate, and when in doubt, should err on the side of a structured note to ensure completeness of documentation.

Some key elements that should be considered in all forms of documentation are that documentation should be:

- Done in a timely manner – ideally during or immediately after care provided.
- Concise – notes should be short and to the point.
- Complete – assumptions should not be made about missing information.
- Avoid dangerous abbreviations – e.g., use "daily" instead of "qd."
- Use professional tone and avoid terms such as inappropriate, unnecessary; avoid judgments or blame for errors.

Conclusion

Utilizing a structured process to approach patient care ensures that pharmacists are both thorough and complete, and that all actual and potential drug-related problems are identified. Assessment starts with interviewing the patient, and creating a database which includes all relevant details of the patient's medical and medication history. From there, the pharmacist can assess drug therapy by considering the four following parameters: indicated, effective, safe, and adherent. After this initial assessment, a care plan can be developed (including recommendations) and implemented with appropriate follow-up and monitoring. Documentation is essential, so practitioners can be accountable for care provided. These are the essential element of the patient-care process which is the heart of the care pharmacists provide.

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Principles of Patient Assessment

2

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Chapter Objectives

1. Describe the role of patient assessment in pharmacy practice.
2. Describe the steps of symptoms assessment.
3. Demonstrate an understanding of chronic disease assessment at both the initial presentation and follow-up.
4. Apply the principles of patient assessment to allergy, adverse reactions, and drug interaction assessment.

Background

The pharmacist's role as health-care practitioner is evolving as pharmacists are taking a more active part in primary patient care. Clinical services are now becoming the forefront of pharmacy practice as pharmacists are helping patients manage their medications and diseases, providing patient education, and, in some provinces, prescribing and adapting medications. Pharmacists can be accessed in a variety of practice settings—for example, in community pharmacies, in the hospital, and in specialized practices. This wide range of practice settings gives pharmacists the opportunity to be involved in patient care for a variety of patients, from those who are acutely ill to those in long-term care. Pharmacists' involvement in patient care can make a significant difference to clinical outcomes and patient care and can decrease medication-related adverse events.

Pharmacists are the health-care professionals most accessible to the public. Patients frequently approach pharmacists with their health-related questions. Many of these questions center around patients with acute minor illnesses who request a pharmacist to help them select an over-the-counter product. Furthermore, frequent visits to the pharmacy for medication refills provide an opportunity for pharmacists to have regular follow-ups with patients and to be involved in chronic disease management. Finally, as the medication experts, pharmacists have a significant role in ensuring safe medication use for each patient throughout his/her treatment course. All of these roles require pharmacists to be familiar with and capable of providing patient assessment.

Patient assessment is the process of methodically collecting information while also using clinical judgment and therapeutic knowledge to identify patient's actual and potential drug-related problems. The data collected can be objective, such as lab tests or diagnostic imaging, or subjective, such as those obtained from the patient. Patient assessment is a skill that requires an organized process and knowledge of the presenting

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symptom or disease. Pharmacists are required to be able to identify red flags and important patient-specific characteristics throughout the assessment. With this information, the pharmacist can formulate a plan and, if appropriate, provide patient education, a drug or nondrug recommendation, or a referral to another health-care practitioner. Although patient assessment is a clinical task, it also requires strong communication skills, as the patient is a major source of information. The ability to connect with the patient and conduct a patient-centered interview is another facet of a patient assessment that cannot be forgotten.

There are different types of patient assessments due to the wide range of symptoms, diseases, and medications that can be encountered by pharmacists. A symptom assessment could be conducted when a patient presents to the pharmacy requesting a recommendation for a minor ailment, such as a cough. Patients with chronic diseases, such as diabetes, could require a chronic disease assessment at both their initial diagnosis and at regular follow-up visits. In addition, patient assessment involves an approach to assessing adverse reactions, allergies, and drug-drug interactions. Patient assessments are part of the patient care that pharmacists provide and have a significant role in the provision of clinical services.

This chapter provides an overview of patient assessment. Patient assessments specific to a symptom or disease can be found in the respective chapter.

Connection for Effective Patient Assessment

Patient assessment not only relies on the gathering of patient's diseases, medications, physical assessments, and laboratory values but also on gathering a patient's lived experience with the disease and medications [1, 2]. These are often referred to as the illness and medication experience, respectively, and are valuable in identifying the causes of a patient's medication-related problems [3]. A patient-centered interviewing approach, Smith's Patient-Centered Interview: An Evidence-Based Approach, was created to gather lived experiences alongside traditional biomedical information [4]. This model recognizes the complexity of collecting the patient's perspectives alongside specific clinical data. More than 30 years of research indicate that patient-centered interviewing increases clinician job satisfaction, elicits increased patient information, reduces malpractice suits, improves adherence, and improves patient outcomes, including blood pressure and diabetic control [4].

Patient-centered interviewing has three main stages [4]. First, clinicians are first encouraged to connect with the patient and set an agenda followed by patient-centered interviewing to explore patients' illness and medication experiences and the impact on their lives. Pharmacists would invite patients to share their story, encourage the sharing of the personal and emotional context, respond to emotions, and summarize the information to check for accuracy. Pharmacists could explicitly transition to the middle stage with clinical-centered interviewing where the pharmacist would obtain a medical and medication history followed by a physical exam as required. In the end stage, the pharmacist could share information and make a plan.

The quality of patient assessment and patient-centered interviewing depends on pharmacist and patient connection. A high quality of the physician-patient relationship can improve patient health, including measures such as blood pressure, pain scores, and quality of life [5]. While comparable research is not available for pharmacists, patients have requested that pharmacists should recognize them as individuals. Although not all patients feel a need for an ongoing relationship with their pharmacist [6–8], most patients wanted to feel a connection and to be treated with respect in all pharmacist encounters [9]. Establishment of patient connection, whether it leads to a relationship or not, relies on the pharmacist's frame of mind as well as strong communication skills.

Mindful Practice

Pharmacists have been called on to enhance their clinical skills and reduce medication errors by

cultivating a mindful practice [10, 11]. The qualities of a mindful practice include observing one's thoughts and judgments, maintaining curiosity, and acting with compassion [12]. Specifically, in pharmacy practice, Shoemaker suggests that pharmacists should listen to the patient's story, acknowledge individuality, and be curious about one's patient [13]. Mindfulness can be as simple as taking a single deep breath to focus one's self before meeting with a patient and can extend to formal mindfulness practice. A practical and evidence-based approach for professionals has been outlined in Search Inside Yourself [14]. In the health context, limited research suggests that mindfulness training may reduce physician burnout [6] and increase attentiveness [15].

Communication Skills

Patient connections are facilitated by strong pharmacist communication skills, which can be learnt through practice [9]. Connection can be established early in the encounter when pharmacists introduce themselves and take a moment for small talk. These routine greeting rituals recognize a patient as an individual and may lead to insights about a patient's goals and preferences. Pharmacists should use a patient's name, as this shows respect and recognition that again fosters a connection. While these ideas are self-evident, their importance is easy to overlook in a fast-paced practice.

Patients often perceive pharmacists, whether in a community pharmacy, hospital, or clinic, as busy clinicians who may not have time for them. Three specific skills can help pharmacists efficiently create the necessary space for connections: acknowledgement of time, private space, and agenda setting. First, pharmacists can pause and reassure a patient that there is time, despite the fact that the environment may appear busy. Otherwise, patients may choose to save their concerns for another time. Second, pharmacists can offer a private area to talk (if appropriate). Many patients are not aware that pharmacists have space; however, patients are quite aware of the people standing behind or sitting near them who could overhear their conversation. A pharmacist could take the lead by saying "Why don't you come with me to a private area, so we will not be interrupted?" Third, pharmacists could set an agenda even for brief conversations to identify patient questions as well as prevent important questions at the end. Pharmacists can simply ask the patient what they would like to talk about and then follow-up with "what else" until all topics raised. The pharmacist and patient can then agree on what can be discussed at present and what can be scheduled in the future. Patients are often reluctant to raise all concerns, and encouragement helps prioritize issues.

Symptom Assessment

A symptom assessment is a process a pharmacist uses to collect information regarding a symptom a patient is experiencing, such as a cough, sore throat, or a headache. Pharmacists conduct numerous symptom assessments during a single shift. Patients commonly seek pharmacist advice on how to treat their minor ailments and are looking for recommendations on an over-the-counter (OTC) product. Before a pharmacist delves into collecting information on a symptom, it is important to obtain a brief medical and medication history from the patient. This information can affect the questions asked during the assessment and the end recommendation. Throughout the process of the symptom assessment, the pharmacist should be aware of patient-specific characteristics that could affect the pharmacist's advice or plan. Such patient-specific characteristics include age, comorbidities, pregnancy or breastfeeding status, and medication history. Patient-specific characteristics are also important when the pharmacist is assessing for the presence of red flags. A red flag is a symptom or patient characteristic that alerts the pharmacist that there could be a more severe underlying problem and often referral to another health-care practitioner is required. Some examples of red flags would be the presence of a new onset headache at 50 years or older or blood in the stool with diarrhea. If a pharmacist identifies a red flag, it is important to inform

the patient of the next step, which is often seeking additional care. The pharmacist should also advise the patient how urgent the need to seek the attention of another health-care practitioner is, such as the need to make an appointment with his/her family physician or the need to immediately proceed to the emergency department. For patient-specific characteristics and red flags that are relevant to a particular symptom, please refer to the respective chapter related to that topic.

Conducting a thorough symptom assessment is important to get the full history of the symptom, recognize red flags, and make a final recommendation to the patient. Although the goal is to conduct a comprehensive assessment, this can be lengthy and is not always feasible concerning the pharmacy workload or the patient's time. Possible time constraints are why it is important to have a developed process when conducting an assessment, which allows you to gather the information in an organized and efficient manner. An organized process also helps pharmacists know that they have not missed important information during the assessment or on the other hand are repeating questions that will bring forth already known information.

An assessment should begin with an introduction so that the patient knows he/she is speaking to a pharmacist. The next step is to determine the patient's chief complaint and his/her reason for seeking care. It is essential to know the chief complaint before gathering the patient's history as it may help the pharmacist pick-up on key parts of a patient's history or patient characteristics when conducting the rest of the assessment. For example, if the patient has constipation and you begin to conduct a patient history, and he/she is taking opioids for chronic pain then you will be primed to ask specific questions about this possible relationship during the symptom assessment.

Many acronyms have been developed to help health-care practitioners with the assessment process. Some examples of acronyms include LQQOSMA (Location, Quantity, Quality, Onset, Setting, Modifying and Aggravating factors), SOCRATES (Site, Onset, Character, Radiation, Association, Time Course, Exacerbating and Relieving Factors and Severity), and SCHOLAR. In this book, we will be using SCHOLAR. SCHOLAR stands for Symptoms, Characteristics, History, Onset, Location, Aggravating factors, and Remitting factors. Each category in this acronym has a purpose and methodically going through each step will help the pharmacist collect a full history. The first letter is S, for *symptoms*, which is an opportunity to ask about the chief complaint and inquire about any other symptoms the patient may be experiencing. The next letter, C, for *characteristics* focuses on the patient describing the symptom and the pharmacist learning about the quality and severity of the presenting symptom. This part of the assessment is also an opportunity to ask closed-ended questions about the presence or absence of specific characteristics that could also be present. Asking these particular questions can be helpful when determining if any red flags are present. Next, is the *history* section. The goal is to determine how long the patient has been experiencing the symptom and if the patient has experienced this ailment before. A thorough history can be helpful in identifying any red flags regarding the length of time the symptom has been present or its frequency. Also, if the patient has had the same symptom before it can be helpful to ask about any treatments tried in the past and if they were successful or not. *Onset* asks about when the symptom started and details about this time. This includes what the patient was doing at the time of presentation or if the patient has had any recent changes in his/her life. Determining the onset can help elicit the most likely cause, which could assist in deciding on symtom managment. *Location* seeks to understand where the symptom is located in the body. It may be unnecessary to ask about location if it is obvious, such as with a sore throat or an earache. If the patient is complaining of pain; however, it is important to know the location as well as if the pain is radiating. *Aggravating* and *remitting factors* explore what makes the symptom worse or better and also if the patient has tried any treatment at this point and if that has been successful. Examples of questions in each category can be found in Table 2.1. It is important to note that not all questions will be relevant to every symptom assessment. For specific symptom assessment questions, see chapters on the related topic.

After completion of this process, the pharmacist should have a clear picture of the presenting symptom. Further questioning may be required to gather more specific information if needed.

Table 2.1 Examples of SCHOLAR questions

Part of assessment	Examples of questions
Symptoms	*What is your main symptom?* *Are you experiencing any other symptoms?*
Characteristics	*Describe the symptom* *On a scale of 1–10, how severe is your symptom?* *How often is this symptom present?*
History	*How long have you had this?* *Have you experienced this in the past?*
Onset	*When did it start?* *What were you doing when it started?* *Was it a gradual or abrupt onset?*
Location	*Describe the location of the symptom* *Is there any radiation from this location?*
Aggravating factors	*What makes it worse?*
Remitting factors	*What makes it better?* *Have you tried anything to treat the symptom?*

Additional information gathering such as laboratory test results may be needed for proper assessment. Once the assessment is complete, a quick summary of the data should be presented to the patient. A summary allows the pharmacist to check for accuracy, can help summarize the information, and may be helpful in recognizing additional information that is needed. Finally, ask the patient if there is anything else they would like to add that may have been missed. After the symptom assessment is complete, the pharmacist will be able to create a plan. The plan will be specific to the patient and the symptom and may include a recommendation of pharmacological treatment, a nonpharmacological treatment, or a referral to another health-care practitioner. The recommendation of a drug could be either an OTC product or prescription medication based on the province the pharmacist practices in and its respective scope of practice.

Chronic Disease Assessment

Initial Assessment

Pharmacists have a significant role in the initial assessment of patients who are recently diagnosed with a chronic disease because most often this diagnosis accompanies the initiation of one or more new medications. A new medication requires a thorough assessment by the pharmacist whether at a community pharmacy or in a hospital. This assessment should begin with the formulation of a complete patient history. The history should include patient demographics, medical history, medication history, social history, and allergies. Although the focus of this section is chronic disease assessment, the following overview of an initial assessment can also be applied to transient illnesses. Patients with acute illnesses, such as an infection or anemia, are also initiated on new medications and require an initial assessment by a pharmacist as well. The pharmacist has a responsibility to ensure that the medication is indicated, effective, and safe and the patient can adhere to the treatment. An acronym that can be used to remember these four parameters of assessment is IESA. For a summary of the IESA steps refer to Table 2.2.

Table 2.2 Summary of the steps of a chronic disease initial assessment

Indication	Determine the reason this new medication was prescribed to the patient Assess if the drug is indicated and if medication therapy is currently warranted
Effective	Assess if the drug prescribed is an optimal treatment choice Determine if the dose of medication is appropriate given the chronic disease Consider patient-specific characteristics (e.g., age, comorbidities) Create a plan to monitor for medication efficacy
Safety	Assess if the dose and frequency of the medication prescribed are appropriate for the indication Determine if a medication is safe for the individual patient given the patient-specific characteristics (e.g., age, comorbidities, allergies) Consider the potential for drug interactions Create a plan to address any safety concerns if present Create a plan for continued monitoring of safety
Adherence	The patient is the main source of information on this topic Pharmacist's role is to help brainstorm options to support patient adherence

Indication

After a new medication is prescribed, the pharmacist should initially assess if the new drug is indicated. It is important to determine the reason this new medication was prescribed to the patient. Based on the medication prescribed an assumption of the disease could be made, but it is also important to ask the patient if he/she knows the indication. Asking the patient may present you with an unexpected indication for the medication, as many drugs are used in multiple diseases. After confirmation of the diagnosis, an assessment of the appropriateness of the drug should be made given the chronic disease. It is often helpful to obtain a history of the present illness, as a more detailed history of what led to the diagnosis can be helpful in the initial assessment as well as follow-up. The pharmacist can then assess if the medication is indicated to treat this disease and if medication therapy is currently warranted.

Effective

After confirming the indication, the next step is to assess if the medication has the potential to be effective. The drug needs to be an appropriate choice for the patient's illness. The pharmacist should assess if the drug prescribed is an optimal treatment choice, which can be determined by evaluating if the medication is a first-line therapy option. Many chronic diseases have published clinical guidelines that provide evidence-based recommendations on first-line therapies for the disease. There are cases in which the patient for various reasons is intentionally not prescribed a first-line therapy, and this should be assessed on a case-by-case basis. If the medication is an appropriate option for the chronic disease, the pharmacist can progress to checking the prescribed dose. For a drug to be effective, usually the dose of the medication should be in a particular dosing range. Keep in mind, however, that the recommended dose of a medication can differ depending on the type and severity of the illness. Also, patient-specific characteristics can impact the dose of the medication, and this should be taken into consideration (discussed in the safety assessment section). Finally, prescribers may choose to titrate a medication up to the recommended dose to prevent adverse effects at the beginning of therapy; therefore, the original prescribed dose may be lower than the target. At this point, the pharmacist should also consider how efficacy will be monitored after therapy begins. The monitoring plan may include subjective information from the patient, laboratory tests, diagnostic imaging, or a physical examination. The pharmacist should create a plan to monitor for medication efficacy and inquire if there is a follow-up scheduled with the prescriber. If during this part of the initial assessment the pharmacist judges that the medication and/or its dosage regimen is unlikely to be an effective option, then the next step may be to adapt the prescription or contact the prescriber.

Safety

An essential part of the initial assessment is to assess the safety of the newly initiated medication. Ensuring a drug is safe for patients is the responsibility and one of the main roles of the pharmacist. The first step is to assess if the dose and frequency of the medication prescribed are appropriate for the indication as previously discussed. The next step is to determine if a drug is safe for the individual patient given the patient-specific characteristics. Such characteristics include the patient's age, comorbidities, allergies, and medication history. Certain medications need to be used with caution or are contraindicated in specific disease states or when used concomitantly with other drugs and this can be a safety concern. An example of an interaction with a disease is the use of bupropion in patients with a seizure disorder as it can lower the seizure threshold and therefore is not preferable in those patients. The patient's age is important as it can affect the dose or dosing frequency of the medication; for example, a young child will often require a different dose than an adult. Patient comorbidities can also affect the dose, dosing frequency, as well as medication choice. For example, patients with impaired renal function who have been prescribed a drug that is renally eliminated may require dose adjustments. Allergies can be a significant safety concern, and the pharmacist needs to know if a patient has an allergy before dispensing a new medication. In

addition, an assessment of the compatibility of the new drug with the patient's other medications should occur. Drug interactions can occur among many drugs and can result in ineffective therapy and adverse effects. Furthermore, other patient factors that should be considered are physical characteristics (weight, height, etc.), previous medication intolerances, and the medication's side-effect profile. If the pharmacist is concerned that the drug may be unsafe for the patient, this should be addressed with a plan. This plan may include prescribing or recommending an alternative medication, adjusting the dose or dosing frequency, or contacting the prescriber. Another part of the safety assessment is formulating a monitoring plan. This plan may include future lab tests, such as serum creatinine (SCr) or liver function tests (LFTs). The plan should indicate when the tests need to be done and the health-care practitioner who will be responsible for ordering the test and interpreting the results. A more detailed overview of an allergy, adverse effects and drug interaction assessment are provided later in this chapter.

The chronic disease initial assessment is usually quite comprehensive due to the patient beginning therapy on new long-term medication. Many patients with chronic conditions are also on multiple other drugs and often have other comorbidities, which adds an extra layer of complexity to the pharmacist assessment. This interaction should end with a plan for follow-up and an agreement with the patient on the means of communication (e.g., phone, pharmacy visit) and the approximate time to follow-up (e.g., 2 weeks). For example, a patient starting on an antihypertensive could have a planned follow-up in 2 weeks, so the pharmacist can assess for initial efficacy, the development of adverse reactions, and address any patient concerns or questions.

Adherence

Adherence is an important part of the initial assessment that is often overlooked. If a patient is unable to adhere to medication therapy, then it is unlikely to be effective and might also put the patient at harm. Even before the initiation of therapy, there can be indicators that the patient may have challenges with adherence for a variety of reasons:

- The frequency of medication doses (e.g., three times a day)
- Busy lifestyle
- Low health literacy
- Language barriers
- Problems with dexterity or ability to self-administer medications
- Memory problems or dementia
- Lack of motivation
- Low self-efficacy
- Lack of understanding of the chronic condition

Patients will be the main source of information on this topic, as they are the ones who have to fit the new medications into their schedule. If there is concern regarding nonadherence, the pharmacist's role is to help brainstorm options to support the patient. Adherence can be intentional or nonintentional, and factors that could contribute to either should be part of the assessment. An important consideration when assessing adherence concerns is the frequency of medication doses. For example, if a patient with a busy schedule is starting on a medication that is dosed three times a day, this may be an indicator that adhering to this dosing schedule may be a challenge. Other considerations could be the patient's health literacy, possible language barriers, and the ability of the patient to self-administer the medication. Medication adherence can also be due to a lack of understanding of the disease and the role the medication in its management. All of these potential reasons would require the creation of a plan to help circumvent the possibility of nonadherence. The plan may include, for example, taking the time to write out patient-specific detailed instructions, the use of a translator, blister packing medications, or collaboration with other health-care professionals to arrange assistance in medication administration.

Patient education is important for increasing patients' understanding of their disease, the benefit of the medication, and the potential harms if the disease is untreated. Another com-

mon reason for nonadherence is the medication cost. Pharmacists should consider the cost of the medication to the patient and if the patient will be able to afford to continue to pay for the drug. If this is a concern, options may include generic substitution, switching to a less expensive alternative, or looking into compassionate drug coverage options. Motivation is another key factor to adherence, and it can fluctuate throughout treatment. The diagnosis of a chronic disease and the initiation of a new medication mean that the patient will be asked to make changes in his/her life. This could include changes to a patient's lifestyle, such as exercise or diet, as well as the addition of a new medication into his/her schedule. A patient's motivation for a change can be an indicator of future adherence to therapy. Techniques to increase motivation could include motivational interviewing [18], patient education, and perhaps breaking down lifestyle changes into small gradual steps. Self-efficacy can also be a factor in patient adherence; if a patient does not believe he/she will succeed in making lifestyle changes, this may cause a defeated attitude and lack of motivation from the beginning. Similar techniques to motivational interviewing can be used to help increase self-efficacy.

Follow-Up Assessment

After a patient's initial diagnosis of a chronic disease and the pharmacist's initial assessment, follow-up assessments are conducted. Patients with chronic conditions require continued assessment throughout their disease course. Patients are often on long-term therapy, and during this time there can be changes in the disease, medications, the patient's lifestyle, and the patient's attitude toward his/her condition. Follow-up assessments allow the pharmacist to evaluate the patients' therapy, provide further education, and discuss patient concerns, questions, and thoughts. Follow-up assessments are conducted at regular intervals that usually coincide with the patient's visits to the pharmacy for medication refills. Follow-up can also occur in the hospital setting for a patient with a previously diagnosed disease or in a clinic with regularly scheduled follow-ups irrespective of the medication refill schedule. More frequent assessment usually occurs soon after the initial diagnosis as patients often have more questions at this time and a pharmacist can address patients' concerns early on. Also, many medication adverse reactions occur soon after initiation of therapy and these reactions should be addressed as quickly as possible. A prompt assessment is required because of the risk to patient safety, and adverse reactions can cause decreased medication adherence. Regardless of when the follow-up assessment happens in the trajectory of the disease, the assessment should focus on four main topics. These areas of focus are adherence, disease control, adverse reactions to the medications, and disease complications; this can be remembered by the two As and two Cs of a follow-up assessment. For a summary of the steps of a follow-up assessment, refer to Table 2.3.

Table 2.3 Summary of the steps of a chronic disease follow-up assessment

Adherence	Nonadherence can lead to disease complications and a lack of disease control Pharmacists should be nonjudgmental during this discussion with patients Work with the patient to discover his/her barriers to adherence and discuss possible solutions
Disease control	Assess to determine if medication is currently effective at treating the specific chronic disease Can include both objective (e.g., lab tests) and subjective data collected from the patient
Adverse reactions to the drug	Assess early on and throughout the entire course of treatment May require a change to the medication, the dose or referral to another health-care practitioner if severe
Disease complications	Often an indication that the current therapy is not effective or potentially that the disease is progressing Requires a reevaluation of the current treatment and potentially a change in medication, dose, or an addition of a new medication

Adherence

As discussed earlier, pharmacists play a vital role in the assessment of a patient's adherence to treatment. A pharmacist can assess a patient's adherence to both pharmacological treatments and nonpharmacological therapy, such as lifestyle changes. Adherence is important to assess as nonadherence can lead to disease complications and a lack of disease control. It is important to note that adherence can change throughout treatment, which is why it should be assessed at each follow-up visit. Adherence can be intentional and nonintentional, but pharmacists should be nonjudgmental or criticizing during this discussion with patients. Pharmacists should work with the patient to discover his/her barriers to adherence and discuss possible solutions that the patient believes may help, such as alarms, dosettes, etc.

Disease Control

An assessment of disease control should occur at each follow-up as it provides evidence of the efficacy of the current pharmacological and nonpharmacological therapies. This part of the assessment can include both objective and subjective data collected from the patient. Objective information could include lab tests (e.g., hemoglobin A1C for diabetic patients), diagnostic imaging, or the occurrence of an event (e.g., stroke, seizure). Collecting information from the patient is often a helpful source to facilitate assessment of disease control. Patients can provide information on the presence of disease symptoms, home test readings if applicable (e.g., blood pressure), and their thoughts on the control of their condition. Depending on the disease, this part of the assessment may be more focused on objective or subjective data. For example, to assess the disease control of a patient with hyperlipidemia, the pharmacist would be looking almost solely on lab test results. This example can be contrasted to a patient with chronic pain where the pharmacist would rely on the patient's account of his/her pain control. If the disease is not adequately controlled, then changes in therapy may need to occur, such as a medication change, change in dose, or an addition of another medication.

Adverse Reactions to the Medication

Adverse drug reactions are often assessed early on, but also need to be continued to be evaluated throughout the entire course of treatment. Some medications' adverse reactions do not occur for months to years after the initiation of therapy. Pharmacists play an essential role in monitoring and managing adverse medication reactions. Adverse reactions can range from mild to very severe and need to be addressed as they are a safety concern and can cause decreased adherence to therapy. If a patient is experiencing an adverse reaction, a medication or dose change may be required, or if the reaction is severe, a referral to another health-care practitioner for treatment may be needed. A pharmacist should be aware of red flags that would prompt referral to another health-care professional. An example would include a patient on an NSAID that presents with blood in the stool.

Disease Complications

Complications of the disease should also be assessed at each follow-up. Disease complications can include the occurrence of an event (e.g., myocardial infarction) or a worsening of symptoms. Disease complications are often an indication that the current therapy is not effective or potentially that the disease is progressing. Identifying red flags is important for assessing the need for referral to another health-care practitioner. An example would be the presence of a diabetic foot ulcer in a diabetic patient.

Follow-up assessments give pharmacists the opportunity to continue to assess a patient's medication therapy and disease control. If there are no concerns at the time of assessment, this assessment can often be brief with no changes required. If there are concerns or complications, the pharmacist can address this by formulating a plan to either modify medication treatment, refer the patient to another health-care professional, or provide patient education.

Allergy Assessment

Patient's allergies should always be kept on the patient's health-care or pharmacy file. When a pharmacist encounters a new patient, the pharmacist must ensure that a full list of the patient's allergies is collected. Also, when a patient has been prescribed a new medication, the pharmacist should always check that the patient's allergy information is up to date so that an allergy assessment can be conducted. An allergy assessment is used to determine a patient's "true" allergies and their accompanying reactions. With the knowledge of the patient's drug allergies, the pharmacist can ensure the safety of the drug for the patient. An allergy assessment not only prevents morbidity and mortality, but it also can prevent the unnecessary use of less appropriate therapeutic alternatives. Adverse reactions or intolerances to drugs can often be mislabeled as allergies. Determining if a patient has a "true" drug allergy prevents a prescriber from avoiding certain drugs that may be better therapeutic options for the patient. Allergies usually present as one or all of the following symptoms: urticaria, skin eruptions, bronchospasm, angioedema and/or anaphylaxis. The presence of these symptoms is evidence that the patient has an allergy to the drug. Intolerances that are labeled as an allergy are often gastrointestinal-related such as stomach upset, nausea and vomiting, or diarrhea. Other adverse reactions that are reported as allergies are dizziness, drowsiness, or delirium.

When a patient starts a new medication, the pharmacist should either have or compile a list of the patient's allergies and the reaction he/she experienced. Just writing down a list of allergies without determining the symptoms the patient had is a common cause for intolerances being mislabeled as allergies. The pharmacist should also ask when in the patient's life he/she last experienced the allergic reaction. The time period is important because there are allergic reactions that some patients may outgrow as they become adults, such as a penicillin allergy. Also, the pharmacist should establish a timeline of the symptoms including the date the drug was dosed, the length of therapy, and the date the allergic reaction occurred. Determining a timeline helps the pharmacist evaluate if the allergy was likely due to the drug or due to other causes. Finally, the pharmacist should ask if the patient has ever had the drug allergy rechallenged. If the patient did receive the drug again and there was no allergic reaction, then the drug is likely safe for the patient to receive again.

If it is determined that the patient had a previous allergy to a drug, then the next step is to create a plan on how to manage this potential drug-related problem. If the reaction was mild, such as a minor skin rash, then the best option may be to rechallenge the allergy. If the patient is willing to rechallenge, then the pharmacist should provide education on the signs and symptoms of an allergic reaction and follow-up with the patient in a few days to ensure no reaction has occurred. The patient may not be willing to rechallenge the allergy due to fear of a reaction, and a therapeutic equivalent may need to be prescribed. If the previous allergic reaction was severe, such as angioedema, anaphylaxis, or Stevens-Johnson syndrome, then choosing an alternative drug would be the safest option. There are cases, however, where the drug that has been prescribed is a far superior therapeutic option or even the only option. In these cases, a risk-versus-benefit analysis can be conducted, and if the benefit of the drug outweighs the risk of the allergy, then there are desensitization protocols that can be ordered under the supervision of a physician.

Another aspect of an allergy assessment is cross-sensitivity, which is the concept that an allergy to one drug predisposes an individual to have an allergy to another drug with a similar chemical structure. There are reports of cross-sensitivity reactions between drugs, but the risk is often quite low. For example, the risk of a patient with a penicillin allergy experiencing an allergic reaction with a cephalosporin is <2% [16]. The pharmacist should evaluate the risk for cross-sensitivity with the use of evidence and clinical judgment. Often the risk of cross-sensitivity is low, and the pharmacist can dispense the drug as prescribed and provide patient education on the signs and symptoms of an allergic reaction. If the past drug allergy was severe and the

cross-sensitivity between the other drug is non-negligible, then a risk-versus-benefit analysis should be conducted.

If a patient is currently experiencing an allergic reaction at the pharmacy or home, then the first step is to assess the severity of the reaction. If the reaction is self-manageable, such as urticaria or a mild skin rash, then the pharmacist could suggest an OTC product like diphenhydramine. Referral to another health-care practitioner may be required if the reaction is severe, such as if the patient is having trouble breathing. Inform the patient of the level of urgency that is needed in seeking additional care, if the allergy is life-threatening, 911 should be called. At this time or the patient's next visit to the pharmacy, the pharmacist should discuss the cause of the reaction with the patient. Asking the patient about any recent new medications or changes to medications can help determine if the reaction was drug-related. Any drug allergies need to be recorded in the patient's file along with the type of reaction that the patient experienced. The pharmacist should also inform patients to alert their other health-care providers. If a patient has an allergic reaction to a medication and has not completed the course of therapy, a decision needs to be made to continue or discontinue the medication. The decision can depend on the severity of the allergy, the patient's wishes, and the length of treatment remaining. If a replacement drug is required, then the pharmacist should discuss with the prescriber alternative therapeutic options, preferably not in the same class of drug.

The following are some examples of common drug allergies. These drugs should alert pharmacists to be especially diligent in their allergy assessment:

- Acetylsalicylic acid
- NSAIDs
- Antiepileptics
- Sulfonamides
- Beta-lactams
- Opioids

Of note, other drugs not listed can also lead to allergic reactions, as well as fillers in medications, such as lactose. Educating patients about the signs and symptoms of an allergic reaction may increase the ability of the patient to recognize a reaction and seek treatment quicker.

Adverse Drug Reaction Assessment

An adverse drug reaction (ADR) is an unwanted response to a drug that occurs at standard therapeutic doses. As the drug experts, pharmacists are essential in preventing ADRs and in creating recommendations and plans to help circumvent an ADR if it arises. In order to avoid potential ADRs, a crucial step a pharmacist can take is to conduct a thorough patient history, symptom assessment, or chronic disease assessment. Knowledge of these factors allows the pharmacist to identify potential drug-related problems before the patient even begins therapy and the pharmacist can adapt the treatment based on any concerns. Patient-specific characteristics such as age and weight can impact the dose of the drug or can predispose a patient to an ADR. For example, elderly patients prescribed a sedative, such as zopiclone, may be predisposed to experience an ADR such as falls. When a patient begins a new medication, the pharmacist should always educate the patient on the common ADRs and potential severe ADRs. A monitoring plan should be set, e.g., what laboratory tests to be ordered and how often and who will follow up with the test results. At each follow-up visit, patients always need to be asked if they have noticed any ADR; this can include open-ended questions or closed-ended questions asking about a specific common ADR of a drug. Any ADR experienced by the patient should always be recorded on his/her file with the name of the drug and the specific reaction.

If a patient presents to the pharmacy during a follow-up or comes to discuss a possible ADR, an assessment is required to determine if it was drug-induced. There are several factors that determine if the symptoms the patient is experiencing are likely to be ADRs:

- Temporality: After the pharmacist has a clear idea of the presenting reaction, he/she can

Table 2.4 Naranjo adverse drug reaction probability scale

Question	Yes	No	Unknown	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	−1	0	
5. Are there alternative causes that could on their own have caused the reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total score			
Total score	*Interpretation*			
≥9	Definite			
5–8	Probable			
1–4	Possible			
≤0	Unlikely			

Adapted with permission from John Wiley and Sons. Naranjo CA et al. [17]

begin to determine if a drug is the cause. A pharmacist may suspect an ADR if the patient was recently started on a new medication or the dose of the medication was recently changed. For a drug to be the cause, there has to be a timeline that is consistent with the presentation of the reaction. On the other hand, if the patient experiences the symptoms before drug initiation, the patient's newly started medication is not likely the cause. It is important to remember, however, that ADR can occur months to years after a medication was initiated.

- The reported reaction fits with the drug's possible ADRs: Another consideration is to check if the reaction or pattern of the reaction fits with the literature and what has been reported previously.
- Biologically plausible based on the drug's mechanism of action.
- The reported reaction disappears or reverses after medication discontinuation.
- There is no alternative explanation of the patient's reported adverse reaction.

After this assessment, the pharmacist can establish the probability of the reaction being drug-related. Table 2.4 depicts Naranjo adverse drug reaction probability scale, a tool to check the probability if the reaction is drug-induced [17]. Based on the scores calculated from the scale, the pharmacist may label it as definite, probable, possible, or unlikely. If the symptom or reaction is deemed to be not drug-induced, an assessment should be made to help determine the cause, and a plan for treatment or referral should be made.

ADRs can be dose-related or nondose-related. ADRs fall under any of the following categories:

- Allergic reactions (not dose-related)
- Idiosyncratic (unpredictable reactions that are not dose-related)
- Drug toxicity (generally dose-related; occurs with drug overdose)
- Side effects (could be acute or chronic; dose or not dose-related)
- Drug withdrawal symptoms
- Drug interactions (see next section)

Once an ADR has been confirmed, pharmacists can create a management plan. The plan may consist of continuing the drug and providing patient education if the reaction is mild or is known to be transient and the patient is willing to continue therapy. Some ADRs can also be resolved with patient education, such as if the ADR is likely caused by how the patient is administering the medication. Some medications require the patient to take the drug with food to avoid gastrointestinal discomfort. Assessing if the patient is taking the drug with food could be the key to finding an easy solution to the ADR. Other plans may include dose reduction or suggesting an alternative therapy. If the drug causing the ADR is clinically required and there are no therapeutic alternatives, then a benefit vs. risk analysis should be performed to determine if continuing the drug has a more significant benefit to the patient than the harm caused by the drug. Regardless of the recommendation, the plan should be documented in the patient's file for future reference. In the future, if the same or similar drug is prescribed to the patient, the ADR could be rechallenged depending on the severity of the original ADR and how necessary the drug is and the availability of therapeutic alternatives and with shared decision-making with the patient.

Drug Interaction Assessment

Drug-Drug Interactions

A drug-drug interaction occurs when a drug affects the pharmacokinetic or pharmacodynamic profile of another drug. Pharmacists have a key role in the identification and the management of drug-drug interactions. For a pharmacist to be able to assess a drug interaction, a complete patient medication history is needed that includes prescription and over-the-counter medications, as well as any supplements or vitamins. A drug interaction can occur via multiple mechanisms. One common type of drug interactions is when one drug alters the metabolism of another drug by inhibiting or inducing an enzyme (e.g., cytochrome P450 (CYP450)). Drugs can also affect other pharmacokinetic properties such as absorption, distribution, and excretion from the body. Moreover, pharmacodynamic drug-drug interactions are possible. Concomitant administration of drugs might lead to synergistic, antagonistic, or de novo effects. Regardless of the mechanism, drug interactions can lead to detrimental effects such as an increased risk of adverse events or therapy failure. Pharmacists have an important role in being able to assess their patient's medications for potential drug interactions to prevent the significant clinical impact an interaction can have. It is difficult for a pharmacist to be familiar with all the possible interactions due to the existence of so many drugs and drug combinations; however, it is important for pharmacists to be educated on the common drug's interactions that are seen in their practice site. Also, to help assist the pharmacist, most pharmacies have medication management software programs that can identify potential drug interactions and alert the pharmacist who can then make an assessment.

Drug interactions can range from not clinically significant to severe; a pharmacist needs to be able to identify where an interaction falls on this scale to be able to make an appropriate plan. Generally, interactions that are not clinically significant do not require an intervention. A method for managing some interactions can be the separation of the administration times of the two medications. Many of these interactions are due to a drug affecting the absorption of another due to altering the environment of the gastrointestinal tract or through binding or chelation. An example is the need to separate levothyroxine administration from calcium- or iron-containing products by 4 h due to decreased absorption if administered together. It is paramount that a pharmacist can recognize interactions and make an appropriate plan especially some drug interactions can be severe and even fatal. A plan for severe interactions may include changing a medication to a safe alternative or separating the administration of the drug by a period of time. An example of a clinically significant interaction is the dangerous hypotensive effect when sildenafil and isosorbide

mononitrate are combined. The potential for this interaction makes it imperative that patients separate the two medications by at least 24 h. Some severe interactions can involve multiple drugs, and the addition of another drug can exponentially increase the risk of an adverse event. An example of this is the potentially fatal combination of multiple drugs that prolong the corrected QT interval (QTc) interval, such as ondansetron, citalopram, and quetiapine. If the patient must be on a combination of these drugs, often a baseline electrocardiogram (ECG) is warranted. After a pharmacist has identified a potential drug interaction, an appropriate intervention should follow. An intervention could include patient education, a medication substitution or dose change, a test for a patient's baseline status (e.g., ECG), therapeutic drug monitoring, or contacting the prescriber. The pharmacist should also consider patient-specific characteristics when deciding on an intervention. Older age, polypharmacy, and baseline factors such as renal or hepatic function can influence the likelihood of a patient experiencing an interaction.

Ideally pharmacists can prevent drug interactions from occurring; however, not all drug interactions can be averted. Consequently, pharmacists will be faced with situations in which a patient is presenting with a drug interaction that has already occurred. Pharmacists should consider a drug interaction as a potential cause of an adverse event if the patient is taking more than one medication. An examination of the patient's medication list and inquiring about any nonprescription medication and supplements will allow the pharmacist to either rule out an interaction or prompt a more thorough investigation. If a drug interaction is thought to be the cause, steps should be taken to resolve this drug-related problem. A referral will be needed if the interaction is severe and the patient may require immediate medical attention.

There are a vast number of drugs that can be implicated in drug-drug interactions. Table 2.5 depicts some examples of classes of medications or supplements that are known to cause drug interactions. Depending on the pharmacist's practice site, some of these medications may be seen frequently or rarely if at all. Pharmacists should familiarize themselves with the classes of drugs that are frequent culprits of drug interactions at their practice sites. Note that not all drugs in each medication class listed may cause drug interactions, as well as each medication in class, may not produce an interaction to the same degree.

Table 2.5 Classes of medications that are major perpetrators of drug-drug interactions

Anticoagulants	Fluoroquinolone antibacterials
Antidepressants	HMG-CoA reductase inhibitors
Antiepileptics	Macrolide antibacterials
Antineoplastic agents	Protease inhibitors
Antirejection agents	St. John's Wort
Antituberculosis agents	

HMG-CoA 3-hydroxy-3-methyl-glutaryl-coenzyme A

Drug-Food Interactions

A drug-food interaction assessment is often approached differently than drug-drug or drug-disease interactions. Pharmacists can identify a potential drug-drug or drug-disease interaction when the medication is initially prescribed. Pharmacists can create a plan to change the drug, dose, or duration of the therapy based on this initial assessment because they have access to the patient's medication and medical history. On the other hand, pharmacists are unable to conduct a similar assessment with drug-food interactions because a patient's complete diet history is not available. At medication initiation, the pharmacist can ask the patient questions about his/her diet and meal schedule. However, most of the pharmacists' role will be to provide education to the patient on potential drug-food interactions and how to mitigate this risk. For example, risedronate needs to be taken 30 min before food intake. Drug-food interactions can range from mild to severe depending on the type of the interaction, the drug, and the quantity of the specific food that is ingested. Drug-food interactions are predominantly due

to the effect of food on the absorption of the drug and can include both solid food as well as drinks (e.g., juice and alcohol). Some drugs have better absorption with food in the stomach, such as amoxicillin/clavulanate, and are recommended to be taken with meals. Other drugs are absorbed less when taken with food and should be taken on an empty stomach, such as bisphosphonates. Food can also affect the metabolism of drugs and can act as an inducer or inhibitor of enzymes. One of the most documented examples is grapefruit and its inhibition of the enzyme, CYP3A4. Inhibition of CYP3A4 decreases the metabolism of drugs metabolized by CYP3A4, such as simvastatin, tacrolimus, and felodipine. Food can also enhance the effects or side effects of some drugs, such as the increased sedation with alcohol and benzodiazepines, or counteract the effect of the drug, such as with vitamin K and warfarin. An example of a clinically significant drug-food interaction is the combination of metronidazole and alcohol. This combination can cause a disulfiram-like reaction, which produces symptoms ranging from nausea to tachycardia and hypotension. Examples like metronidazole and alcohol show the importance of pharmacist counseling and patient education when a patient is initiated on medication with the possibility of a drug-food interaction.

Some examples of food and drinks that are commonly implicated in drug-food interactions can be found in Table 2.6. This list is not exhaustive but provides a few examples of drugs that interact with a particular food or drink.

Table 2.6 Examples of food-drug interactions

Food or drink	Drugs and mechanism of interaction
Alcohol (many alcoholic beverages contain tyramine; see foods that contain tyramine.)	*Antiepileptic drugs* (e.g., carbamazepine), *benzodiazepines, narcotic analgesics* (e.g., morphine), *sedatives* (e.g., zopiclone): Synergistic effect leading to increased risk of adverse effects, such as CNS depression *Isotretinoin*: May enhance the adverse effects of the drug, such as an increased risk of elevated triglyceride concentrations *Metronidazole*: May enhance the adverse effects of alcohol and can cause a disulfiram-like reaction
Caffeine	*Ciprofloxacin, fluvoxamine*: Can increase the serum concentration of caffeine *Lithium*: Decreased serum concentration of the drug, which may diminish the therapeutic effect of the drug *Clozapine*: Increased serum concentration of the drug leading to possible toxicity *Theophylline*: Synergistic effect leading to increased risk of adverse effects
Foods high in calcium (e.g., milk)	*Allopurinol, bisphosphonates, cefuroxime, dabigatran, fosinopril, levothyroxine, quinolone antibacterials, tetracycline antibacterials*: May decrease the absorption and the serum concentration of the drug, which may diminish the therapeutic effect
Foods high in potassium (e.g., bananas)	*ARBs, ACEIs, potassium-sparing diuretics*: May enhance the hyperkalemic effect, which can cause adverse effects such as muscular weakness, fatigue, arrhythmias, and bradycardia
Foods high in tyramine (e.g., strong or aged cheese)	*MAOIs*: May cause a hypertensive crisis
Foods high in vitamin K (e.g., dark, leafy green vegetables)	*Warfarin*: May diminish the therapeutic anticoagulant effect
Grapefruit (including juice)	*Amiodarone, clopidogrel*: May decrease the serum concentration of the drug, which may diminish the therapeutic effect *Antirejection agents (*e.g.*, sirolimus), DHP calcium channel blockers, HMG-CoA reductase inhibitors*: May increase the serum concentration of the drug leading to possible toxicity

ARBs angiotensin II receptor blockers, *ACEIs* angiotensin-converting enzyme inhibitors, *MAOIs* monoamine oxidase inhibitors, *DHP* dihydropyridine, *HMG-CoA* 3-hydroxy-3-methyl-glutaryl-coenzyme A

Table 2.7 Examples of drug-disease interactions

Drug	Disease
Anticholinergics	*Constipation*: Due to slowed gastrointestinal motility and decreased secretions from the intestinal tract *Dementia*: Has been associated with greater cognitive decline *Glaucoma*: Can narrow the drainage angle of the eye and prevent eye fluid from properly exiting the eye resulting in high eye pressure *BPH*: Reduces bladder muscle contractions and can aggravate BPH symptoms
NSAIDs	*Hypertension*: Can elevate blood pressure *Peptic ulcer disease*: Lowers prostaglandin levels and damage the gastroduodenal mucosa *Chronic renal disease*: Lowers prostaglandin levels, which causes decreased blood flow and oxygen supply to the kidneys
Bupropion	*Seizures*: Can lower the seizure threshold
Benzodiazepines	*Dementia*: Increased risk of confusion and delirium *Falls*: Can cause sedation and daytime drowsiness; the risk is greatest in elderly patients
Beta-blockers (specifically noncardioselective beta-blockers)	*Asthma*: Can cause bronchoconstriction and worsening of asthma symptoms
Non-DHP calcium channel blockers	*Heart failure*: Weaken the force of muscular contractions (have a negative inotropic effect) and can exacerbate heart failure symptoms and worsen the condition

NSAIDs nonsteroidal anti-inflammatory drugs, *BPH* benign prostatic hyperplasia, *DHP* dihydropyridine

Drug-Disease Interactions

Pharmacists also need to be aware of potential drug-disease interactions. A drug-disease interaction is an interaction that occurs between the drug and one or more of the patient's comorbidities. It can lead to an increased or decreased effect of the drug or can aggravate the disease or its complications or lead to adverse drug effects. A complete medical and medication history is required for proper drug-disease interaction assessment. If there is a potential for a drug-disease interaction, a plan should be formulated, which may include changing the medication or the dose, or careful monitoring of the disease. An example of such interactions that may be encountered in practice is renal insufficiency. Renal impairment can significantly impact the elimination of renally excreted drugs. A renal dosage adjustment or medication avoidance is often recommended in patients with decreased renal function. In addition, some drugs have nephrotoxic potential and should be used with caution. Patients with impaired renal function and taking renally eliminated drugs or those on nephrotoxic drugs should have their kidney function assessed regularly throughout therapy.

Table 2.7 depicts examples of some common drug-disease interactions. This table is not exhaustive but is meant to provide a few examples of drug-disease interactions that a pharmacist could come across in practice. It is important to note that OTC drugs could be potentially implicated in drug-disease interactions. Counseling is important and pharmacists should ask patients to seek advice if they are starting any OTC medication or herbals. An initial chronic disease assessment can provide an opportunity to educate the patient on OTC medications he/she should avoid.

Conclusion

Pharmacists expanding scopes of practice and emerging clinical roles allow the pharmacists to conduct patient assessments daily for a variety of symptoms, and acute and chronic diseases. Pharmacists can individualize and adapt the patient assessment process to their specific practice needs. They need to make sure that each medication is indicated, effective, and safe for every patient and that the patient can adhere to the treatment. Patient assessments conducted by

pharmacists make a difference in patient safety, clinical outcomes, and improve patient-centered care. The following chapters in this book provide a detailed approach to patient assessments that focus on individual symptoms or chronic diseases followed by specialized topics in patient assessment.

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3 Physical Assessment for Pharmacists

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Chapter Objectives

1. Outline the basic steps involved in physical assessment (PA).
2. Complete a general survey and review of systems for a specific patient.
3. Describe how PA can be used in pharmacy practice to enhance pharmaceutical care.
4. List available comprehensive guides to physical assessment, so that one can begin to develop new PA skills as they evolve in their practice.

Background

Physical assessment (PA) is used by healthcare professionals to gather important information about their patients. For example, physicians and nurse practitioners (NPs) use PA as part of their comprehensive assessments and for diagnosis and management plans. Nurses on the hospital ward do physical assessments every shift to monitor the health status of acutely ill patients. Pharmacy practice can be enhanced with the use of PA as well. It is useful for the initial and follow-up assessment of patients and in monitoring response to therapy and adverse drug reactions. In addition, PA aids in identifying red flag signs and symptoms that prompt referral to other healthcare practitioners or the emergency department. Each practice area will lend itself to a different set of skills, and each pharmacist can determine for themselves which skills will be useful in their own practice. Compared to other professions, pharmacists have a unique perspective and scope of practice. They generally do not perform a comprehensive physical examination [1]. For this reason, this chapter will focus on specific skills and activities that can be used to identify drug therapy problems, and to gather information that a pharmacist can use in the provision of pharmaceutical care. Resources such as "Bates' Guide" or "Patient Assessment in Pharmacy Practice" [1, 2] are available as comprehensive guides to the abundance of PA skills and activities that have been established in the medical, nursing, and other fields. Since physical assessment involves many specific terms that may not be familiar to all pharmacists, a glossary of terms is found in Table 3.1.

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Table 3.1 Glossary of terms

Glossary term	Meaning
Accessory muscles	Muscles in the shoulders and chest that are not used in normal breathing but are used by patients who are in respiratory distress or having trouble breathing
Adventitious	Abnormal, as in abnormal lung sound
Anaphylaxis	Severe, IgE-mediated allergic reaction that involves bronchoconstriction, wheezing, itching/hives, facial/throat/tongue swelling, low blood pressure, and gastrointestinal symptoms like vomiting, diarrhea, and abdominal pain. It usually starts within minutes to hours of exposure to the allergen
Anterior	The front side of the body (toward the stomach)
Apical heart rate	Measured at the bottom (apex) of the heart by auscultation of the area where the fifth intercostal space and the mid-clavicular line intersect
Bronchial breath sounds	Louder, harsher sounds that are heard when the large bronchi are auscultated; also heard when a patient has pneumonia and consolidated lungs
Bronchovesicular breath sounds	Normal sounds in the mid-chest area or between the scapula and reflect air moving through mid-sized airways. They will be between the pitch of bronchial and vesicular sounds
Conjunctivitis	Inflammation of the conjunctiva in the eyes
Cyanosis	Blue-tinged skin caused by lack of oxygen
Delirium	Acute disturbance in state of mind and mental processes that is characterized by incoherent thoughts and speech, restlessness, and illusions. Often related to fever, intoxication, or other physical disorders
Dentition	The teeth and how they are arranged in the mouth
Dermatome	An area of skin that is innervated by a single spinal nerve
Encephalopathy	Altered function of the brain from damage, disease, or other malfunction, usually presents as altered mental state
Exudate	A combination of fluid, cells, and pus that has been deposited in tissue after escaping from intact blood vessels. It usually occurs due to inflammation
Gastroenteritis	Inflammation of the stomach and intestines due to a multitude of causes. Symptoms are usually nausea, vomiting, and diarrhea
Hives	Itchy, raised patches of skin that can be reddish or pale. Due to an IgE-mediated reaction to allergens or other stressors and will disappear after the trigger is removed
Hypoxia	Lack of oxygen
Jaundice	Yellow-colored skin or sclera of the eyes due to buildup of bilirubin. Often associated with liver damage
Lymphedema	Lymph fluid accumulating in tissues, usually the legs, and producing swelling
Mottled	Skin that is blotchy or irregularly colored. It is often due to inadequate perfusion, or cold
Myxedema	Synonymous with severe hypothyroidism, but also describes the skin changes that occur with hypothyroidism including swelling and thickening of the tongue and mucous membranes
Neuralgia	Nerve pain or painful spasms; often described as burning, shooting, aching, and following a certain nerve
Neuritis	Inflammation of a nerve and tends to feel like burning pain
Nystagmus	Flickering, spasmodic, involuntary movement of the eyes
Posterior	Toward the back of the body
Pruritus	Itching of the skin
Rhinorrhea	Watery, mucous discharge from the nose
Sternal angle	The angle formed by the manubrium and the sternum which provides an anatomical landmark. This landmark provides an "outer edge" of the thoracic plane and is where the jugular venous pressure is measured against
Sympathomimetic	Producing an effect similar to that of the sympathetic nervous system. Usually associated with increased heart rate and blood pressure, pupil dilation, sweating, piloerection
Syncopal (syncope)	Temporary loss of consciousness due to lack of blood supply to the brain with paleness, sweating, nausea, and blurry vision

Table 3.1 (continued)

Glossary term	Meaning
Toxidrome	A collection of symptoms that occur when a patient is exposed to toxic levels of a certain type of substance. They help you to rapidly rule in or out a possible causal substance in an unknown intoxication
Turgor (skin)	Elasticity of the skin and ability to return to normal shape after it is stretched
Vesicle	Raised, fluid-filled lesion on the skin, usually smaller than 0.5cm across (if larger than 0.5cm, called a bulla)
Vesicular breath sounds	Normal breath sounds that are soft and low pitched. They have a rustling quality and are louder at the bases of the lungs because they reflect air movement in the terminal bronchioles and alveoli
Wernicke's encephalopathy	The combination of altered mental status, abnormal gait, and nystagmus caused by thiamine deficiency. Usually associated with alcohol use disorder or malnutrition
Wheals	Well-defined areas of edema in the skin that are usually itchy and reddened

Physical Assessment Introduction

Physical assessment (PA) is the evaluation of objective anatomic findings gathered through four distinct activities, *inspection*, *palpation*, *percussion*, and *auscultation* [3], which are done in the stated order. However, not all of the above activities are needed each time a physical assessment is done [1]. The objective information gathered through PA is considered in combination with the subjective information gathered from the patient's health history. Together with the general survey, the health history and PA comprise the overall health assessment of a given patient [1].

Inspection involves the use of vision, hearing, and smell to examine patients or the specific area that is being assessed. Inspection is usually used in conducting a general survey (see below) and it yields important information that should be deliberately noted as one examines the patient [1].

Palpation uses the hands to feel for abnormalities on the surface or deeper if required. One should start with light palpation and move deeper as needed, for example, to feel the size of internal organs or to feel for tenderness. Palpation is used to measure a pulse, assess peripheral edema, or feel for palpable lymph nodes, as examples [1].

Percussion involves lightly striking the body surface with the purpose of producing a sound. For example, to percuss the lungs, one would place their index or middle finger on the patient's skin and then lightly strike that finger with the other hand. The sound that is produced provides clues about the nature of underlying tissue. For example, a louder sound is produced by the air-filled lungs, in comparison to the solid biceps muscle [1]. This technique could be used to identify an area of consolidation in a patient with suspected pneumonia, where dullness may be heard.

Auscultation is the act of listening to the sounds created by the body, usually using a stethoscope. Auscultation can be performed on the heart, lungs, blood vessels, and viscera. Chest auscultation yields important information. Lung and heart sounds can provide important clues about serious illnesses. Examples of abnormalities that can be heard via auscultation include heart murmurs, extra heart sounds, lung crackles, decreased air entry, carotid bruit, apical heart rate (HR), etc. [1]. These abnormalities often signal a need for medical attention.

General Survey

Note the patient's physical appearance, behavior, and mobility. The general survey can tell us a great deal and is easy to perform. It can be performed while casually speaking with the patient. The following are key pieces of information to be gathered during the general survey [4]:

- *Appearance*: Overall appearance, hygiene, grooming, attire, skin color, presence of lesions, height, and weight

- *Behavior*: Facial expressions, level of consciousness, orientation, speech, and demeanor
- *Mobility*: Posture, range of motion, use of mobility aids, and gait

Vital Signs

Vital signs provide vital information. Generally, the term "vital signs" includes blood pressure, heart rate, respiratory rate, and temperature. Many practice settings also include oxygen saturation. Every pharmacist should be able to interpret a patient's vital signs as reported by other healthcare professionals. Ideally, pharmacists should be able to perform vital signs measurement themselves as well. Table 3.2 shows normal ranges in adults for the vital sign parameters. Vital signs for children, infants, and neonates should be looked up in references specific to these age groups, and further information about vital sign assessment in pediatric patients is found in Chap. 28.

Blood Pressure

Blood pressure (BP) measurement is a particularly important assessment, and one that is prone to inaccuracy due to external factors (see Chap. 13 "Hypertension" for more details). Proper BP measurement is the first step to managing hypertension, as well as BP-related adverse effects from medications. Since some patients will not monitor their BP independently, pharmacists should try to offer measurement to all patients whose BP could have therapeutic relevance. See Table 3.3 for the recommended techniques for BP measurements [5].

Table 3.2 Normal ranges for vital sign parameters in adults [1]

Vital sign parameter	Normal range
Blood pressure	SBP: ~120–140 mmHg DBP: ~80–90 mmHg
Heart rate	~60–100 bpm
Temperature (varies by measurement method)	~36.1°C–37.2°C (fever generally considered to be >38°C)
Respiratory rate	~12–20 bpm
Oxygen saturation	~95–100% considered normal <90% generally considered low For patients with COPD requiring oxygen therapy, desired range is usually 88–92%

COPD chronic obstructive pulmonary disease, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

Pharmacists play a key role in managing hypertension. By helping patients monitor and interpret their BP, pharmacists help to mitigate risks and maximize benefits of drug therapy. Research has shown that pharmacist prescribing for hypertension management leads to clinically and statistically significant reductions in BP [6]. Pharmacists are also well-positioned in the healthcare system to detect BP-related drug therapy problems. For example, heart failure (HF) patients are usually on multiple drugs that affect their BP, such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and diuretics. HF patients often have BP in the lower range, but these "BP" medications are titrated up in order to get to evidence-based doses for maximal morbidity and mortality benefit. Pharmacists can help HF patients get the most from these medications by assessing each scenario when patients have questions about their BP and medications. If a patient is tolerating a dose and is not symptomatic, then a lower BP may not be problematic. Conversely, for patients who are experiencing adverse effects while their medications are uptitrated, the pharmacist may be the first healthcare provider to know about it through follow-up assessment. Further assessment of hypertension is found in Chap. 13.

Heart Rate

Heart rate (HR) is another important parameter. For patients with HR outside the normal range of 60–100 beats per minute (bpm), one should ask the questions "What is causing the abnormality?" and "Is this problematic?" For example, a person who is very fit may have a resting HR < 50–60 bpm due to cardiovascular adaptations from exercise. This is "normal" for them, and not concerning. For a patient who is taking a beta-blocker, bradycardia (HR < 60 bpm) may

Table 3.3 Recommended techniques of BP measurements[a]

Recommended technique for automated office blood pressure (AOBP)
1. Measurements should be taken with a validated sphygmomanometer known to be accurate 2. Choose a cuff with an appropriate bladder size matched to the size of the arm. Select the cuff size as recommended by its manufacturer 3. Place the cuff so that the lower edge is 3 cm above the elbow crease and the bladder is centered over the brachial artery. There is no rest period needed before measurement. The arm should be bare and supported with the BP cuff at heart level, as a lower position will result in an erroneously higher SBP and DBP. There should be no talking, and patient's legs should not be crossed 4. When using automated office oscillometric devices, the patient should be seated in a quiet room (no specified period of rest), with the device set to take measures at 1- or 2-min intervals. The first measurement is taken by a health professional to verify cuff position and validity of the measurement. The patient is left alone after the first measurement, while the device automatically takes subsequent readings 5. Record the average BP as displayed on the electronic device as well as the arm used and whether the patient was supine, sitting, or standing. Record the heart rate
Recommended technique for office blood pressure measurement (non-AOBP)
1. Measurements should be taken with a sphygmomanometer known to be accurate. A validated electronic device should be used. If not available, a recently calibrated aneroid device can be used. Aneroid devices or mercury columns need to be clearly visible at eye level 2. Choose a cuff with an appropriate bladder size matched to the size of the arm. For measurements taken by auscultation, bladder width should be close to 40% of arm circumference and bladder length should cover 80–100% of arm circumference. When using an automated device, select the cuff size as recommended by its manufacturer 3. Place the cuff so that the lower edge is 3 cm above the elbow crease and the bladder is centered over the brachial artery. The patient should be resting comfortably for 5 min in the seated position with back support. The arm should be bare and supported with the BP cuff at heart level, as a lower position will result in an erroneously higher SBP and DBP. There should be no talking, and patient's legs should not be crossed. The first reading should be discarded and the latter two averaged. BP should also be assessed after 2 min standing (with arm supported) and at times when patients report symptoms suggestive of postural hypotension. Supine BP measurements may also be helpful in the assessment of elderly and diabetic patients 4. When using automated office oscillometric devices such as the BpTRU (VSM MedTech Ltd., Vancouver, Canada), the patient should be seated in a quiet room (no specified period of rest). With the device set to take measures at 1- or 2-min intervals, the first measurement is taken by a health professional to verify cuff position and validity of the measurement. The patient is left alone after the first measurement while the device automatically takes subsequent readings. The BpTRU automatically discards the first measure and averages the next five measures 5. For auscultation, at least three measurements should be taken in the same arm with the patient in the same position. The first reading should be discarded and the latter two averaged 6. Increase the pressure rapidly to 30 mmHg above the level at which the radial pulse is extinguished (to exclude the possibility of a systolic auscultatory gap) 7. Place the bell or diaphragm of the stethoscope gently and steadily over the brachial artery 8. Open the control valve so that the rate of deflation of the cuff is approximately 2 mmHg per heartbeat. A cuff deflation rate of 2 mmHg per beat is necessary for accurate systolic and diastolic estimation 9. Read the systolic level, the first appearance of a clear tapping sound (phase I Korotkoff), and the diastolic level, the point at which the sounds disappear (phase V Korotkoff). If Korotkoff sounds persist as the level approaches 0 mmHg, then the point of muffling of the 10 sound is used (phase IV) to indicate the diastolic pressure. Leaving the cuff partially inflated for too long will fill the venous system and make the sounds difficult to hear. To avoid venous congestion, it is recommended that at least 1 min should elapse between readings 10. Record the BP to the closest 2 mmHg on the manometer (or 1 mmHg on electronic devices) as well as the arm used and whether the patient was supine, sitting or standing. Avoid digit preference by not rounding up or down. Record the heart rate. The seated BP is used to determine and monitor treatment decisions. The standing BP is used to examine for postural hypotension, if present, which may modify the treatment 11. In the case of arrhythmia, additional readings with auscultation may be required to estimate the average systolic and diastolic pressure. Isolated extra beats should be ignored. Note the rhythm and pulse rate 12. BP should be taken in both arms on at least one visit and if one arm has a consistently higher pressure, that arm should be subsequently used for BP measurement and interpretation

(continued)

Table 3.3 (continued)

Recommended technique for home blood pressure measurement
1. Measurements should be taken with a validated electronic device
2. Choose a cuff with an appropriate bladder size matched to the size of the arm. Bladder width should be close to 40% of arm circumference and bladder length should cover 80–100% of arm circumference. Select the cuff size as recommended by its manufacturer
3. Cuff should be applied to the nondominant arm unless the SBP difference between arms is >10 mmHg, in which case the arm with the highest value obtained should be used
4. The patient should be resting comfortably for 5 min in the seated position with back support
5. The arm should be bare and supported with the BP cuff at heart level
6. Measurement should be performed before breakfast and 2 h after dinner, before taking medication
7. No caffeine or tobacco in the hour and no exercise 30 min preceding the measurement.
8. Duplicate measurement should be done in the morning and in the evening for 7 days (i.e., 28 measurements in total)
9. Average the results excluding the first day's readings
Recommended technique for ambulatory pressure monitoring
1. The appropriately sized cuff should be applied to the nondominant arm unless the SBP difference between arms is >10 mm Hg, in which case the arm with the highest value obtained should be used
2. The device should be set to record for a duration of at least 24 h with the measurement frequency set at 20–30-min intervals during the day and 30–60 min at night
3. A patient-reported diary to define daytime (awake), nighttime (sleep), activities, symptoms, and medication administration is useful for study interpretation
4. Daytime and nighttime should preferentially be defined using the patient's diary. Alternatively, predefined thresholds can be used (e.g., 8 AM to 10 PM for awake and 10 PM and 8 AM for nighttime)
5. The ambulatory BP monitoring report should include all of the individual BP readings (both numerically and graphically), the percentage of successful readings, the averages for each time frame (daytime, nighttime, 24 h), and the "dipping" percentage (the percentage the average BP changed from daytime to nighttime)
6. Criteria for a successful ambulatory BP monitoring study are: a. At least 70% of the readings are successful b. At least 20 daytime readings and 7 nighttime readings are successful

BP blood pressure, *DBP* diastolic BP, *SBP* systolic BP. Unless otherwise mentioned, steps apply to measurement by auscultation and oscillometry using an upper arm cuff.

[a]Reprinted from Canadian Journal of Cardiology, 34, Nerenberg et al. [5], Copyright 2018, with permission from Elsevier

warrant dose reduction, depending if they are symptomatic, how low their HR is, and the indication for beta-blocker therapy. For patients who report feeling heart palpitations, or those who are tachycardic (e.g., >100 bpm [1]), one should manually check the patient's pulse to see if it feels irregular. Irregular pulse suggests arrhythmias, such as atrial fibrillation (AF). AF is a common arrhythmia that is described as irregularly irregular. If undiagnosed and untreated, AF puts the patient at risk for stroke and other complications. For patients with an irregular pulse, an ECG is indicated to rule out AF or other arrhythmias. From an infectious disease perspective, tachycardia is one of the signs of sepsis and is cause for concern if any other symptoms are present (RR >20 bpm, SBP < 90 mmHg, temperature > 38 °C, white blood cells (WBCs) >12 × 10^9/L, etc.) [7].

Temperature

Temperature is easy to measure and can be done in any setting. Single-use thermometers are available for purchase and can be used to measure a patient's temperature when applicable. Figure 3.1 shows a commercially available single-use thermometer. The steps for measuring oral temperature with a single-use thermometer are as follows:

1. Wash your hands.
2. Carefully open the package.
3. Insert the thermometer under the patient's tongue, into one of the posterior sublingual pockets. The dots can be facing up or down. Have the patient close their mouth.
4. Wait 60 seconds.

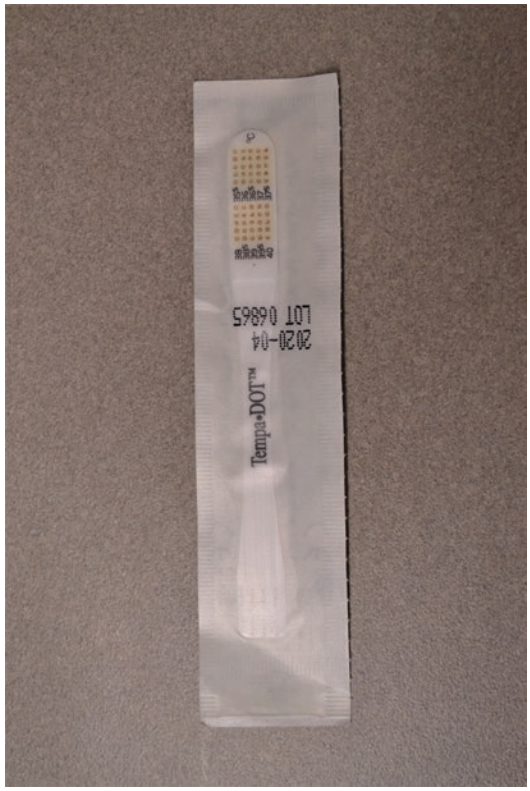


Fig. 3.1 Example of commercially available single-use thermometer

5. Remove thermometer and wait 10 seconds before reading.
6. Read the temperature by determining the last blue dot on the matrix. Record temperature.

In addition to the oral route, temperature can be measured by the axillary, rectal, tympanic, or temporal artery route. Table 3.4 depicts the normal temperature ranges and considerations for the various routes.

Table 3.4 Temperature measurement by different routes [1]

Temperature route	Normal temperature in adults (°C)	Comments
Oral	37	Accurate and convenient
Axillary (armpit)	36.5	In adults, this route is used only when oral route not possible
Rectal	37.5	Preferred route if oral not possible (e.g., intubation, facial surgery) Most accurate way to measure core body temperature
Tympanic (ear)	37.5	Noninvasive, quick, and efficient Infrared sensor detects flow of blood through the eardrum
Temporal artery (forehead)	37.5	Measures infrared heat in the temporal artery Next to rectal route, this is the best estimation of core temperature

Respiratory Rate

Respiratory rate (RR) is ascertained visually by noting the rising of a patient's chest to signify a breath, counting the number of breaths in 30 seconds, then multiplying by 2. Alternatively, one may choose to count the number of breaths for the whole minute if the patient is breathing irregularly. Since a person's breathing may be altered if they become aware of it, it is best not to tell the patient when assessing their respiratory rate [1]. Elevated RR can be a sign of respiratory distress, such as in a severe acute exacerbation of chronic obstructive pulmonary disease (AECOPD), asthma exacerbation, or pneumonia. Low RR is also worrisome, as the patient may not be getting adequate gas exchange. They may become hypoxic, or they may develop respiratory acidosis if they are unable to exhale enough carbon dioxide. RR is also an important parameter when monitoring for opioid toxicity. Opioids suppress the body's respiratory drive when taken in excess, an effect which can be fatal. Any patient with low or high RR needs to be referred, possibly even to the emergency room (ER).

Review of Systems

In general, the review of systems is a systematic approach to identifying abnormalities or issues which may not have been identified by

the patient. Each body system is reviewed, often in a head to toe sequence. A review of systems can be completed using focused questioning, PA, and information gathered from other health professionals.

Neurological/Psychiatric

A pharmacist should be familiar with performing and interpreting specific aspects of the neurological exam if it is relevant to their practice. For example, when reflexes are reported, the designations 3+ and 4+ are more exaggerated than normal [1]. This would be relevant when assessing someone for the possibility of serotonin syndrome, since hyperreflexia is one of the possible signs. As well, pharmacists should be looking for signs of neurological concerns such as abnormal movements, abnormal gait, or signs of spasticity as are seen in some patients post-stroke. These may help to assess how well a patient's treatment is working or if there are any adverse effects occurring from medications. One important adverse effect to look for in patients who are using antipsychotics is tardive dyskinesia, which tends to present as repetitive odd movements of the face, mouth, tongue, and head [1].

Level of Consciousness

The general survey provides a good understanding of the patient's level of consciousness (LOC). Decreased level of consciousness, especially a change from baseline, warrants referral to emergency room, or primary care provider if the decrease is mild. For pharmacists working in the hospital setting, it is also helpful to be familiar with Glasgow Coma Scale (GCS). For example, nurses may report GCS as a vital sign in emergency room and critical care areas. Level of consciousness is relevant to medication therapy, as medications that suppress the central nervous system (CNS) may not be appropriate if the patient has a decreased LOC. Additionally, medications could be causing the decreased LOC, and this must be screened for. Patients with decreased LOC also may not be able to swallow medications, and consideration for alternate routes of administration is required if this is the case. Nurses are a great resource to determine whether the oral route is appropriate for a given patient, as they are the individuals who administer medications, and ability to take oral medications is part of their assessment. Table 3.5 shows the rubric for GCS scoring, which is based on the best response the patient gives in each category [8].

Table 3.5 Glasgow Coma Scale (GCS) [8]

Glasgow coma scale component	Best response (with corresponding numerical score)
Eye opening	Spontaneous—4
	To voice—3
	To pain—2
	None—1
Verbal response	Oriented—5
	Confused—4
	Words—3
	Sounds—2
	None—1
Best motor response	Obeying commands—6
	Localizing—5
	Normal flexion (withdrawal)—4
	Abnormal flexion—3
	Extension—2
	None—1

The numerical scores assigned during GCS assessment are typically added together to give a total out of 15, with a range of 3–15. A score of 15 is "normal" and lower scores indicate an altered LOC. Information about how to determine a patient's GCS is available from a variety of resources [9].

Orientation

All pharmacists should be able to check if a patient is oriented to person, place, and time. This should be included in the general survey. Often, this is reported in patient charts as "AO x (number)" which indicates if the patient is alert and how many elements of orientation a patient is able to correctly identify. Simple questions can be used, such as "What is your name?", "Where are we?", and "What is today's date?" It is especially important to get the patient to state what year it is, as some patients may be able to answer all the other questions correctly, and not know what year it is [1]. Assessing orientation helps to

determine if a patient is delirious. In addition to acute confusion, symptoms of delirium include inattention, hallucinations, behavioral changes, etc. Acute confusion or other delirium symptoms warrant referral, as delirium is a medical emergency. The underlying cause of delirium must be ascertained and corrected, if possible. In addition to the need for referral, detecting confusion is helpful if we are trying to gather information from the patient directly, since we may be unable to do so if the patient is significantly confused. Delirium is also an important side effect to look out for from many medications, including benzodiazepines, anticholinergic medications, opioids, or corticosteroids. Monitoring a patient's level of orientation/confusion is also very relevant for the management of hepatic encephalopathy. This is an important efficacy parameter that helps to guide therapy.

Psychiatric

Throughout the physical exam and health history interview, the pharmacist should observe the patient's affect, level of cooperation, etc. Other things to look out for would include suicidal ideation, anxiety, hallucinations, delusions, pressured speech, tangential speech, etc. [1]. Consider one's baseline if they have a history of psychiatric illness. Do not hesitate to ask about specific symptoms if you are concerned about a patient, and have a plan to manage or refer patients who are experiencing psychiatric symptoms. The "Handbook of Clinical Rating Scales and Assessment in Psychiatry and Mental Health" is an excellent resource for mental health assessment [10].

Peripheral Neuropathies

Neuropathies can include a wide variety of conditions that cause damage to either single nerves or multiple nerves in one area. They tend to produce symptoms such as tingling, numbness, pain, and weakness in the affected areas and can be very bothersome to patients. Patients who present with symptoms that suggest neuropathies should be referred to a physician for further assessment, but there are some assessments that pharmacists can perform if trained. Although a neuropathy itself cannot be seen from inspection, many tests can be done to determine if nerve function is intact in an area. These tests assess the patient's ability to feel pain, light touch, temperature, and vibration [1]. Two common tests are the monofilament test and tuning fork test which help to determine the specific deficiencies the patient is experiencing [11]. Often, patients who have long standing or poorly controlled diabetes will develop peripheral neuropathy in their lower limbs. For these patients, daily foot checks can help to catch complications early. Information on how to perform foot checks for patients can be found on the Diabetes Canada website, www.diabetes.ca.

Head, Eyes, Ears, Nose, and Throat

Visually inspect the head, eyes, ears, nose, and throat (HEENT) for abnormalities. In addition, lightly palpate structures on the head, eyes, ears, and nose if it is relevant to your assessment. Examples of notable findings include:

- Dry, flaky, scalp with reddened areas may indicate dandruff, psoriasis, or dermatitis.
- Dry mucous membranes in the mouth, which could be a sign of dehydration.
- Poor dentition, which is a risk factor for many systemic illnesses and poor health in general.
- White patches on the tongue or throughout the mouth can indicate oral candidiasis ("thrush").
- Bulges or swelling in the throat that may indicate a goiter, which can be a sign of hypo- or hyperthyroidism.
- Xanthomas are deposits of cholesterol in the skin of patients who have very high cholesterol levels and indicate a need for referral.
- Tender/swollen cervical lymph nodes can often be felt in patients with pharyngitis.

Eyes

Patients with eye concerns often present to pharmacists in community or other primary care settings for recommendations. By becoming familiar with simple methods of assessing the eyes, pharmacists can improve their patient recommenda-

tions for minor conditions, and are better poised to detect signs of more serious ailments.

When the eyes are irritated, they may appear to be red, with or without discharge. Red eyes may be due to a variety of problems including dry eyes or conjunctivitis. Conjunctivitis may be infectious (viral or bacterial), or it may be noninfectious (allergic, contact lens-related). Patients who have copious discharge likely have infection present and should be seen by a physician or optometrist for appropriate care. For individuals who present with allergic symptoms, including itching and exposure to a known allergen, there are both prescription and nonprescription treatments available. In terms of other infections, patients will often ask for treatment for styes, which are infections of the oil glands that surround the eyelid margin. They will look like bumps right on the margin of the eyelid and may be red and very itchy. The available combination of polymyxin B and gramicidin (Polysporin Eye Drops®) may be effective for some patients but generally it is preferred for them to see a family doctor or optometrist to confirm diagnosis. There is also a relatively high rate of antimicrobial resistance to this product.

Protruding eyeballs, exophthalmos, is a sign of hyperthyroidism. This finding may identify a need for additional therapy if the patient is untreated, or that the dose is too low if they are on treatment already. Serum thyroid-stimulating hormone (TSH), among other more specialized blood tests in conjunction with the clinical picture, can help to interpret this finding.

While assessing the eyes, pay attention to the irises and pupils. First, inspect pupil size. Normal pupils should be equally sized, round, and an appropriate size based on the brightness of the room. Pupils can also change size in response to medications or other substances. Patients who are experiencing opioid toxicity will have pinpoint pupils (miosis). Sympathomimetic drugs often dilate the pupils (mydriasis), which can help to identify causative agents in the setting of an unknown toxidrome. Dilatation of pupils is also a sign of serotonin syndrome, which pharmacists can help identify based on a patient's medication profile.

A pharmacist can also assess eye movement, looking for involuntary oscillating eye movements (nystagmus). Figure 3.2 describes the technique used for assessing eye movements. Nystagmus is relevant to pharmacy practice as it can be a sign of phenytoin toxicity. Also, for patients who present with alcohol use disorder, presence of nystagmus may signal the presence of Wernicke's encephalopathy (WE). The classic triad of symptoms is encephalopathy (disorientation, impaired memory, etc.), gait ataxia, and oculomotor dysfunction. Most patients with WE may have only one or two signs, which makes it harder to diagnose [12]. WE is thought to be underrecognized, and pharmacists can help by seeking out this need for additional therapy.

Rarely, patients can present with what looks like rings around the irises. This may occur in patients with extremely high cholesterol and diseases associated with too much copper (e.g., Wilson's disease) as well as other rare diseases. If it has not been addressed before, this is a sign that the patient needs to be referred.

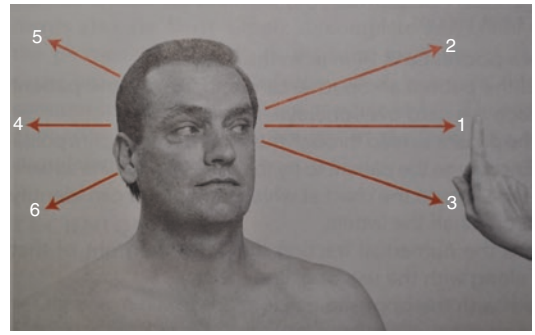


Fig. 3.2 The six cardinal positions for assessing eye movements. Follow these steps to perform the assessment: 1. Instruct patient to follow the movement of your finger with their eyes and not to move their head. 2. Hold your finger ~12–18 inches from the patient's head, starting in the middle. Move your finger to the right side. Watch for a fluttering movement or "beats" of nystagmus with each new position of your finger. 3. From position 1 (right side, midline), move your finger up while staying to the right. This is position 2. 4. From position 2, move your finger down, staying to the right side, to position 3. 5. From position 3, move your finger to the left side, midline, to position 4. 6. From position 4, move your finger upward, staying to the left, to position 5. 7. From position 5, move your finger downward, staying to the left, to position 6. (Reprinted with permission from Jones [1])

Pharyngitis

Pharyngitis is another common complaint that is presented to pharmacists. Patients are often concerned that they have group A streptococcus (GAS) infections, or "strep throat." With the increase in popularity of point of care testing (POCT) for GAS, pharmacists can both display antimicrobial stewardship and for those who do test positive, expedite access to proper treatment. In patients complaining of sore throat, use of a light and tongue depressor will help to visualize the oropharynx (throat), and allow one to inspect for redness, inflammation, and tonsillar edema or exudate.

Palpate the neck area, looking for enlarged or tender lymph nodes. These are usually a sign of infection. While viral pharyngitis is more commonly associated with enlarged posterior cervical lymph nodes, bacterial pharyngitis affects the anterior cervical nodes [2]. However, this is not a guaranteed way to differentiate between the two.

As with all infections, antimicrobial stewardship is an essential component of the pharmacist's role in pharyngitis. For patients with pharyngitis, history and physical examination findings are very helpful to differentiate between a viral and bacterial source. In general, the presence of URTI viral symptoms such as cough, conjunctivitis, gastroenteritis, or rhinorrhea indicates a viral infection. Patients with any symptoms of viral infection should not undergo testing such as rapid antigen detection testing (RADT) for group A streptococcus (GAS) pharyngitis. Careful selection of patients for microbiological testing is an essential step in avoiding unnecessary antibiotic therapy. Since many people are asymptomatic carriers of GAS, a swab in a patient who has viral symptoms could easily lead to a false positive result. Signs and symptoms of GAS pharyngitis include acute onset sore throat, plus the factors included in the Centor criteria [13, 14]. These criteria also provide a threshold score above which RADT is indicated and below which GAS pharyngitis is unlikely. The modified Centor criteria include age, and are presented in Table 3.6.

When ≥3 criteria are present, RADT is recommended. Less than three criteria indicates that GAS pharyngitis is unlikely [13]. For patients with symptomatic, confirmed GAS pharyngitis (RADT + follow-up culture), antibiotics are usually prescribed. Although GAS pharyngitis is usually self-limited (~8–10 days), antibiotics reduce severity and duration of symptoms. They also reduce transmission, and complications such as peritonsillar abscess, and acute rheumatic fever [15].

Table 3.6 The modified Centor criteria for probability of group A strep pharyngitis [13, 14]

Criterion	Score		
Age	3–14 y (+1)	15–44 y (0)	≥45 y (−1)
Tonsillar swelling or exudate	Yes (+1)	No (0)	
Tender or swollen anterior cervical lymph nodes	Yes (+1)	No (0)	
Temperature > 38°C	Yes (+1)	No (0)	
Absence of cough	Yes (+1)	No (0)	

Dermatological

Inspection and palpation are the main modes of PA of the skin. Since much of the information will be collected from inspection, it should be performed in a well-lit room with either natural light or the ability to use a penlight to determine how raised a lesion is. Fluorescent light tends to make lesions appear flat [1]. When performing palpation, gloves are important both for patient comfort and practitioner safety. Patients may present with a rash, wart, or other specific dermatologic concern. One can inspect the area, looking closely for distinguishing features. Careful, focused history taking will play an important role in dermatologic assessment as well. Included with skin assessment is assessing the hair and nails. Changes to the nails can be a sign of autoimmune disorders, such as psoriasis, or infection if splinter hemorrhages are present. Nails that are very thick, lifting up from the nail bed or are discolored can be a sign of a fungal infection. These are often found in older patients and on the toenails.

One rare but serious condition that pharmacists must be diligent in screening patients for is anaphylaxis, as this condition is a potential reaction to vaccines and other medications. Patients may ask their pharmacist when early anaphylaxis symptoms are present either right after receiving an injection or by phone after taking a new medication. Signs and symptoms include hives/wheals, pruritus, flushing, hypotension, difficulty breathing, nausea, vomiting, headache, and dizziness [1].

Another condition which may be encountered by pharmacists is shingles (herpes zoster). Shingles typically starts as neuritis/pain over a certain region, and usually progresses to a rash over a specific dermatome, often with the development of vesicles [1]. Early recognition is key, as early treatment (<72 h from onset of symptoms) speeds up resolution of rash, vesicles, and pain, as well as reduces transmission to others. It may also reduce residual pain from postherpetic neuralgia [16, 17].

When assessing a patient, the pharmacist should take note of the patient's skin color. For example, the skin or sclera may have a yellow hue, which may be caused by a buildup of bilirubin due to liver dysfunction. This is known as jaundice. Bluish or purplish discoloration of the lips or fingers, also known as cyanosis, is a sign of hypoxia. Pale looking skin can indicate underlying anemia or could also occur in a person who is about to have a syncopal episode. Mottled skin, which looks like blotchy purple discolorations, can be a sign of several things including shock. Alteration in skin color may also be due to adverse effects of medications. One of the most striking is "blue man syndrome" caused by amiodarone. This will appear as a bluish discoloration in sun exposed areas in patients who have used the drug for a long time or at high doses. Oral contraceptives can also be associated with discoloration in the form of hyperpigmented patches called chloasma. Both types of discoloration can improve on their own after the drug is withdrawn but it may take months. They are usually harmless but can be distressing to patients as they often occur on the face.

Decreased skin turgor, which is a sign of dehydration, is detected by pulling up on the skin. If the skin remains elevated in a tent-like formation, this is decreased skin turgor. Other physical symptoms that can be observed with dehydration include dry mucous membranes and eyes. Dehydration requires referral for further evaluation.

The temperature of the skin can be felt using the back of the hand. Notice if it is warm, cool, dry, or clammy. This may be considered with other symptoms the patient is experiencing in determining a diagnosis. For example, if a patient has a red, swollen, hot area of skin, they may be experiencing an infection in that area.

For further assessment, we refer the reader to Chap. 11. It discusses dermatological assessment in more detail.

Respiratory System

Assessment of the respiratory system yields important information. Pharmacists should be familiar with general landmarks used to describe respiratory findings, as can be found in Figs. 3.3, 3.4, and 3.5. Aside from determining the patient's respiratory rate, the pharmacist can also use inspection to assess for use of accessory muscles during respiration. This can be seen as muscles in the neck contract with each breath, lifting the ribs and sternum to allow a larger volume of air to enter the lungs [1]. If not associated with exercise, accessory muscle use can be a sign of respiratory distress. Tripod breathing, when a patient leans forward and puts their hands on their knees, is another sign that can indicate respiratory distress and is often seen in patients with emphysema. Barrel chest is another abnormality which can be visualized. It is caused by overinflation of the lungs and can be seen in patients with chronic obstructive pulmonary disease (COPD), or old age [1]. These patients will have a chest that is at least as wide from back to front as it is from left to right.

Auscultation of the lungs is a useful skill. Ideally, the lungs should be auscultated from the anterior and posterior aspects. Have the patient breathe slowly and deeply through their mouth. Using the diaphragm of the stethoscope (larger

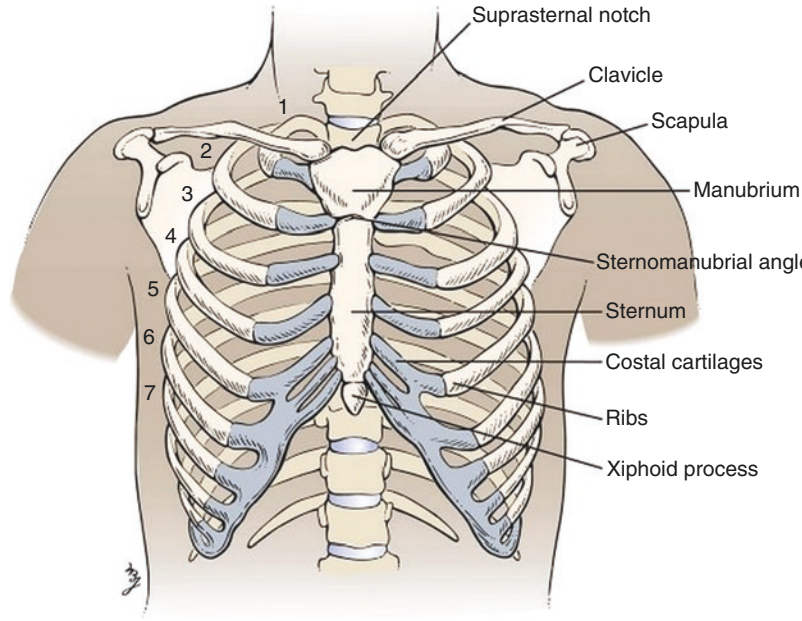


Fig. 3.3 Cardiac and respiratory landmarks for physical assessment: Bony chest skeleton. (Reprinted from Textbook of Physical Diagnoses, 7th ed., Swartz MH, The chest, 315–342.e1, Copyright 2018, with permission from Elsevier)

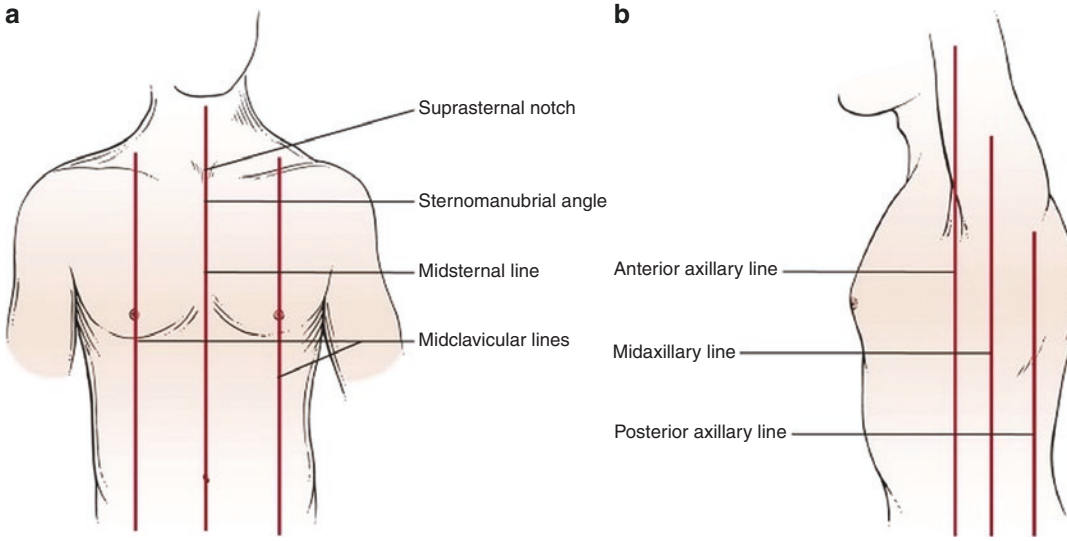


Fig. 3.4 Cardiac and respiratory landmarks for physical assessment: Thoracic cage landmarks. (**a**) Topographic landmarks of the anterior thorax. (**b**) Landmarks on the lateral view. (Reprinted from Textbook of Physical Diagnoses, 7th ed., Swartz MH, The chest, 315–342.e1, Copyright 2018, with permission from Elsevier)

side of round listening surface), auscultate each lung field, moving from upper to lower fields. Figure 3.6 depicts correct stethoscope positioning on the posterior thorax, to ensure that each lobe is listened to. Listen to a full breath cycle at each position before moving to the next. One should be familiar with the normal breath sounds prior to looking for abnormal (adventitious) sounds. Depending on where one places their stethoscope, they will hear bronchovesicular, vesicular, or bronchial breath sounds. Each has a characteristic sound, owing to the underlying structures

(main bronchi, bronchioles, lobes, and trachea). The Internet hosts many educational websites (e.g., www.easyauscultation.com) which provide audio samples of both normal and adventitious breath sounds. Table 3.7 depicts examples of adventitious breath sounds.

Patients with respiratory conditions will often have spirometry testing done to determine the degree of airflow limitation they have. Patients with COPD should have this done during diagnosis, as well as whenever an exacerbation is suspected. Pharmacists should be aware that a post-bronchodilator forced expiratory volume over 1 second (FEV1) over forced vital capacity

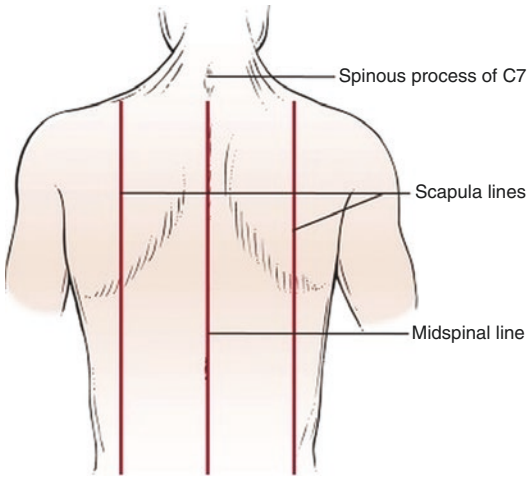


Fig. 3.5 Cardiac and respiratory landmarks for physical assessment: Topographic landmarks of the posterior thorax. (Reprinted from Textbook of Physical Diagnoses, 7th ed., Swartz MH, The chest, 315–342.e1, Copyright 2018, with permission from Elsevier)

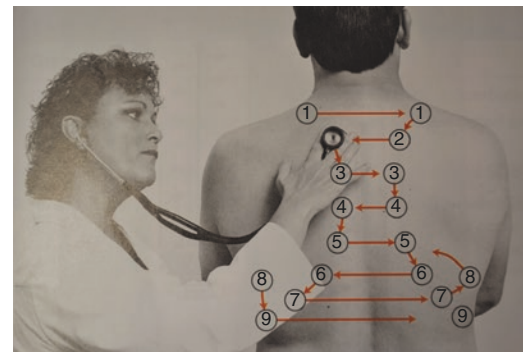


Fig. 3.6 Auscultation points for breath sounds. (Reprinted with permission from Jones [1])

Table 3.7 Adventitious lung sounds [1, 2]

Adventitious sound	Characteristics of sound	Clinical correlation
Crackles (fine or coarse)	Intermittent, nonmusical, and brief Fine crackles are soft, high pitched, and very brief Coarse crackles are louder, lower-pitched, and longer	Caused by fluid, mucus, or pus in the airway Fine crackles can be heard in pulmonary edema (HF), pulmonary fibrosis Coarse crackles can be heard in pneumonia, COPD, lung abscess, TB
Rhonchi	Low-pitched, rattling lung sound with snoring quality. Mostly heard with expiration. Usually clears after coughing	Caused by obstruction or secretions in larger airway Can be heard in COPD, pneumonia, bronchitis, etc.
Wheezes	High-pitched, long, musical sound Can be heard with expiration or inspiration	Caused by airway narrowing Can be heard in asthma, COPD, and bronchitis
Friction rub	Grating or creaking sound that can usually be localized on the chest wall and can come and go	Inflamed pleura rubbing together is the cause, with friction arising from lack of lubricating fluid Any condition associated with pleural irritation can cause this, such as pneumonia
Stridor	High-pitched, musical sound. Can often be heard without a stethoscope	Caused by upper airway obstruction Can be heard in patients upon extubation

COPD chronic obstructive pulmonary disease, *TB* tuberculosis

Table 3.8 Classification of COPD airflow limitation based on post-bronchodilator FEV1 [18]

Degree of limitation	GOLD class	FEV1 measure in comparison to expected value
Mild	1	≥80%
Moderate	2	50%–<80%
Severe	3	30%–<50%
Very severe	4	<30%

COPD chronic obstructive pulmonary disease, *FEV1* forced expiratory volume over 1 second, *GOLD* Global initiative for chronic obstructive lung disease

(FVC) ratio (FEV1/FVC) value <0.7 is supportive of a COPD diagnosis. This means that after the patient is given a bronchodilator, they still have airflow limitation present [18]. Patients will have different degrees of airflow limitation (Table 3.8), which contributes to their classification between mild to severe disease in combination with other symptoms and degree of functional limitation. See Chap. 16 for more detailed information about COPD assessment.

In asthma, many patients use a peak flowmeter, which assesses how quickly they can blow air out of their lungs. An example of one available peak flowmeter is shown in Fig. 3.7. Patients should know what their peak flow is when they are not experiencing any symptoms, as a decrease can show a worsening in asthma control. From a pharmacy perspective, patients who have asthma and use a peak flowmeter could have their normal value recorded while completing a care plan in order to monitor disease progression. See Chap. 15 for more detailed information about asthma assessment.

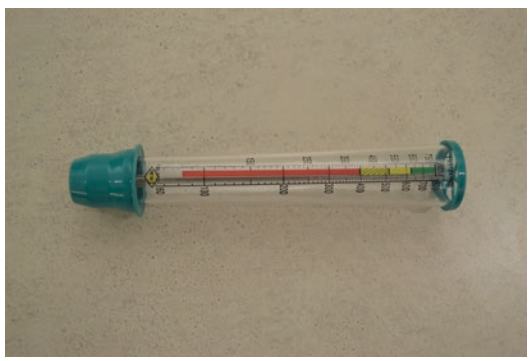


Fig. 3.7 Example of a peak flowmeter

Cardiovascular/Peripheral Vascular System

As discussed above, BP and HR are measured during the assessment of vital signs. Both of these values are important and are taken into consideration alongside the cardiovascular exam. During the general survey, the pharmacist should take note of how the patient is mobilizing, and whether they experience any dyspnea with movement or at rest. This is especially relevant to patients with HF. If a patient reports chest pain, this requires referral for further assessment. Auscultation of the heart will reveal an abundance of information about the patient's cardiovascular system; however, most pharmacists are not trained to perform this. Some pharmacists who are in specialty practice, such as heart function clinics, may be trained to perform more advanced cardiac assessments. One example of how auscultation can be used is in patients with atrial fibrillation; the apical heart rate may be more accurate than measuring the peripheral pulse, since not every heartbeat will be transmitted peripherally. To illustrate, the peripheral pulse may be 80 bpm, but the apical rate could 105 bpm, with the extra beats lost in transmission. Apical rate could help to guide therapy if one is adjusting the patient's rate control to a resting target of <100 bpm. The heart sounds are also important to consider. All pharmacists should be aware that S1 and S2 sounds (corresponding to the closing of the heart valves) are normal, and the presence of additional sounds can indicate pathologies such as heart failure. Cardiac murmurs are also detected via auscultation. There is a grading system based on their qualities and intensities, from I to VI, faint to very loud [1]. A new cardiac murmur, taken in context with the patient's clinical picture, could be a sign of infective endocarditis, for example. This finding could affect antibiotic choice or dose, depending on the situation. Being aware of these findings and their implications when they are reported will allow pharmacists to optimize patient care whether or not they are able to perform the assessments themselves.

Assessment of the patient's QT interval is also relevant in patients who are on certain

medications or have certain medical conditions. It will be reported if a patient has an electrocardiogram (ECG) done, but pharmacists should also be aware of when it should be requested in patients who have never had an ECG. Most pharmacists are not trained to interpret an ECG tracing, but it is important to be familiar with what a normal interval is, as well as factors that are known to prolong it. A normal rate corrected QT interval (QTc) is <430 ms for men and <450 ms for women. Many medications have an impact on the QT interval, including some anti-infectives, antidepressants, antiarrhythmic drugs, and drugs of abuse. Factors such as electrolyte imbalance, age, sex and cardiovascular disease add to the risk [1]. Patients with prolonged QTc interval are at higher risk of an arrhythmia known as Torsades de pointes (TdP) which can cause sudden cardiac death. Therefore, when the QTc interval exceeds 450 ms males and 470 ms in females, it is imperative to address any modifiable factors including electrolyte correction and changing medications. There are many resources available to determine a patient's risk of QT prolongation, including www.crediblemeds.org, which will allow you to consider multiple risk factors together.

Circulation can be assessed by palpating peripheral pulses. One should make note if the pulse is normal, diminished, or absent. As an example, a person with peripheral arterial disease (PAD) may have diminished peripheral pulses, a person who is experiencing shock may have absent pulses [19]. Figure 3.8 shows the various sites for palpating peripheral pulses.

Volume Status

The patient's volume status is a key consideration for pharmacists, whether the patient is euvolemic, hypovolemic, or hypervolemic. For example, patients with hypovolemia are at risk for acute kidney injury, and they may accumulate any medication that is renally cleared. They are also at higher risk of toxicity from nephrotoxic drugs. For patients who take diuretics, fluid status is essential for appropriate dosing, to ensure maximal efficacy and minimal toxicity. Volume status is also central to determining etiology for patients with hyponatremia, a condition that frequently has implications for drug therapy. There are several PA skills that can help determine a patient's level of hydration. Inspection is used to examine the mucous membranes and skin turgor as discussed previously. Additionally, one would inspect the lower extremities for the presence of peripheral edema. Palpation is used to confirm the presence of edema, and to determine whether it is pitting or not. If edema is present at the ankle level, one would inspect and palpate up the leg to see how high the edema goes. This is an important finding to note, as it is an indicator of the degree of fluid overload. Pitting edema is graded on a numeric scale, from 1+ to 4+, with 1+ being least severe. If the edema is nonpitting, it is usually due to either lymphedema or myxedema. One should also note whether the edema is bilateral and symmetrical. Unilateral edema could be due to deep vein thrombosis or venous insufficiency, for example [19].

Of note, peripheral edema is a common side effect of calcium channel blockers (CCB). For example, up to 15% of non-HF patients taking amlodipine experience peripheral edema [20]. The risk is higher in women than in men and is also higher with dihydropyridine vs. non-dihydropyridine CCBs. The effect is likely dose dependent and tends to build up gradually. Venodilators can counteract CCB-induced edema. Angiotensin-converting enzyme (ACE) inhibitors are the most studied class for this indication [21].

Another important aspect to volume status assessment is the jugular venous pressure (JVP), as this is a marker of right atrial pressure, as well as central venous pressure. This can be a challenging skill to master, in part because the visibility of veins is variable [1]. However, even if one is not proficient at estimating JVP, it can still be useful to know how to interpret the results. The normal range of the JVP is ~3–4 cm above the sternal angle. Values <3–4 cm would suggest hypovolemia, and values greater than 4 cm indicate hypervolemia [1, 2]. JVP assessment is frequently performed by physicians and NPs during

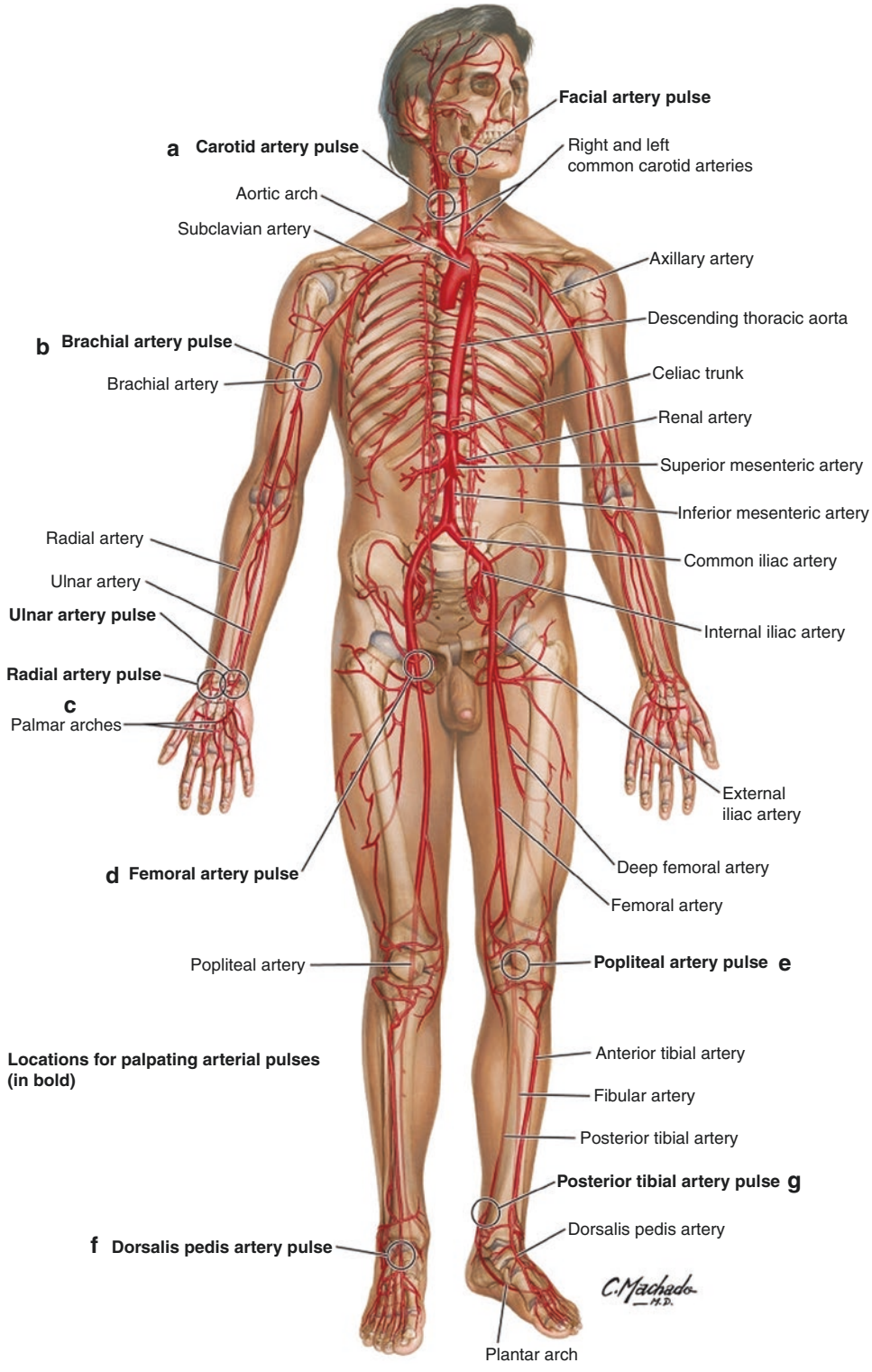


Fig. 3.8 Palpation of arterial pulses, (**a**) carotid, (**b**) brachial, (**c**) radial, (**d**) femoral, (**e**) popliteal, (**f**) dorsalis pedis, (**g**) posterior tibial. (Reprinted from Atlas of Human Anatomy, 7th ed., Netter FH, Chapter 1: Introduction, Plates 4, 11–10, Copyright 2019, with permission from Elsevier)

care for patients with HF and other medical conditions (see Chap. 14: Heart Failure).

Genitourinary, Renal, and Gastrointestinal Systems

For patients with genitourinary, renal, or gastrointestinal complaints, focused health history taking will be the main mode of information gathering. A structured approach to questioning, such as SCHOLAR, will help to ensure comprehensiveness. Review of laboratory findings plays an important role as well. Assessments of the liver and kidneys are explored in Chaps. 23 and 24, respectively.

Liver function should be considered, as many drugs are metabolized by the liver. Advanced liver disease puts patients at high risk for adverse effects from medications, such as bleeding or encephalopathy/delirium. The Child-Pugh classification is a validated scoring system which considers both lab values and physical findings in order to categorize patients based on their degree of liver dysfunction. The categories are A, B, and C, with A being milder dysfunction, and C being severe liver disease. One of the physical findings that can often be seen is ascites, as patients' abdomens can be very large with fluid accumulation. Child-Pugh score can be used to determine whether dose reduction of medications is needed, as this is the parameter that is often used for drug dosing adjustment in liver failure. Online Child-Pugh calculators are readily available [22, 23]. There are other clinical scoring systems which are more commonly used for prognostication, such as the MELD (model for end-stage liver disease) score.

Assessing renal function relies on a patient's laboratory values, urine output, and medical history, rather than physical assessment. However, patients who have renal concerns such as stones or infections will often have pain in their lower back that varies in intensity depending on the condition. It is rare to be able to palpate the kidneys well, so this is not often done and other methods of investigation such as ultrasound are preferred [1].

Musculoskeletal

The musculoskeletal (MSK) system has countless possible ailments. The pharmacist is well positioned to screen patients and determine who is appropriate for self-care, and who should be referred on. If the patient is in distress, has decreased mobility, or may require diagnostic imaging, they should be referred to their primary care provider or the emergency room. Depending on one's practice setting and expertise, a pharmacist may use inspection and palpation to assess injuries, including range of motion assessment. For example, pharmacists working in specialty rheumatology clinics will likely use PA and health history taking to complete an in-depth assessment of their patients. However, even those in general practice can inspect joints for signs of swelling and deformities that may indicate rheumatoid arthritis, such as swan neck and Boutonniere's deformities in fingers. Osteoarthritis is another common complaint of patients, but there are few physical signs and often patient assessment will rely on history taking or diagnostic imaging. Within the same differential diagnosis as different types of arthritis can be gout. In most patients, this will present as a single red, inflamed, acutely painful joint. It is often the first metatarsal-phalangeal joint of the foot. Patients who present with this picture should be referred to their physician for further assessment and diagnosis.

Adverse effects of medications can manifest as MSK symptoms as well. One important area that pharmacists should be familiar with is statin-induced muscle symptoms. These are a common complaint among patients taking statins. Figure 3.9 presents an assessment tool which may be used to help determine if muscle symptoms are due to the statin [24].

Patients who have osteoporosis with damage to the spine will often have abnormal curvature of their spine, called kyphosis, as a result of vertebral compression fractures. Upon inspection, they will have a hunched back in the shoulder area. They can also have a shortened distance between their rib cage and pelvis. If a patient cannot stand up straight against a wall with their head and

Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)

Instructions:

- Use with patients who have had muscle symptoms that were new or increased after starting a stating regimen.
- A statin regimen includes any statin at any dose or frequency, including a statin the patient has used previously, at the same or a different dose.
- Muscle symptoms may include aches, cramps, heaviness, discomfort, weakness, or stiffness.
- Interpret overall score in light of other possible causes of the muscle symptoms, such as:
  - Recent physical exertion
  - Changes in exercise patterns
  - Hypothyroidism
  - Drug interaction with statin
  - Concurrent illness
  - Underlying muscle disease
- See reverse for Frequently Asked Questions

How many statin regimens has the patient had that involved new or increased muscle symptoms?

One
Complete the questions on the left side of this page.

Two or more
Complete the questions on the right side of this page.

Regarding this statin regimen:

A. Location and pattern of muscle symptoms (if more than one category applies, record the highest number.) — **Enter score:**

Symmetric, hip flexors or thighs	3
Symmetric, calves	2
Symmetric, proximal upper extremity	2
Asymmetric, intermittent, or not specific to any area	1

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3
4–12 weeks	2
>12 weeks	1

C. Timing of muscle symptom improvement after withdrawal of statin (if patient is still taking statin, stop regimen and monitor symptoms.)

<2 weeks	2
2–4 weeks	1
No improvement after 4 weeks	0

Rechallenge the patient with a statin regimen, (even if same statin compound or regimen as above) **then complete final question:**

D. Timing of recurrence of similar muscle symptoms in relation to starting second regimen

<4 weeks	3
4–12 weeks	1
>12 weeks or similar symptoms did not reoccur	0

Total: All four scores above must be entered before totaling

Regarding the statin regimen *before* the most recent regimen:

A. Location and pattern of music symptoms (if more than one category applies, record the highest number.) — **Enter score:**

Symmetric, hip flexors or thighs	3
Symmetric, calves	2
Symmetric, proximal upper extremity	2
Asymmetric, intermittent, or not specific to any area	1

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3
4–12 weeks	2
>12 weeks	1

C. Timing of muscle symptom improvement after withdrawal of statin

<2 weeks	2
2–4 weeks	1
No improvement after 4 weeks	0

Regarding the *most recent* statin regimen:

(even if same statin compound as above)

D. Timing of recurrence of similar muscle symptoms in relation to starting regimen

<4 weeks	3
4–12 weeks	1
>12 weeks or similar symptoms did not reoccur	0

Total: All four scores above must be entered before totaling

Interpretation

Total score:	2–6	7–8	9–11
Likelihood that the patient's muscle symptoms are due to statin use:	Unlikely	Possible	Probable

10 Oct 2016, Based on Rosenson et al. An assessment by the Statin Muscle Safety Task Force: 2014 update, *J Clin Lipidol.* 2014 May-Jun;8(3 Suppl);S58–71.

Fig. 3.9 Statin-associated muscle symptom assessment. (Reprinted from Springer Nature under the terms of Creative Commons CC BY license from Rosenson et al. [24])

shoulders on the wall, it can be a sign of kyphosis. Vertebral compression fractures can also be screened for by simply asking how tall they were when they were 20 years old and how tall they are now. Losing >2.5 inches from age 20, or >2 inches in a year is a sign that they need further assessment [25]. Osteoporotic patients may also have fractures from falls that are not expected to be damaging. These are often hip or forearm fractures caused by trying to break a fall. In patients who present after these types of fractures, a risk assessment can be done to decide if they need further screening or treatment for osteoporosis.

Lab Work and Microbiology

The pharmacist should review pertinent laboratory values and microbiology when required, as this can have a significant impact on drug therapy. Each unique clinical scenario will dictate what lab work is needed. The following are some of the tests that are frequently applicable to pharmacy practice:

- Blood work:
  - Complete blood count (CBC) with or without differential,
  - Serum electrolytes ("lytes"),
  - Urea (BUN),
  - Creatinine (SCr),
  - "Liver function tests" (alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and conjugated), international normalized ratio (INR), Alkaline Phosphatase, serum albumin)
  - Thyroid-stimulating hormone (TSH)
  - Creatine kinase (CK)
  - Troponin
  - Lactate
- Drug levels for therapeutic drug monitoring (e.g., phenytoin, valproic acid, vancomycin, gentamicin, digoxin, etc.)
- Urinalysis, arterial blood gas (ABG), venous blood gas (VBG)
- Microbiology: blood, urine, skin and soft tissue, sputum cultures, intraoperative bone/joint/hardware cultures, cerebrospinal fluid (CSF), etc.

Further discussion of laboratory tests is beyond the scope of this chapter. Like all PA and assessment skills, one's ability to interpret lab values is developed through practice and repetition. Resources are available to provide background information about lab tests and their interpretation [26].

Red Flags (Referral Needed)

Screening for red flags during physical assessment is a broad but important topic. A comprehensive list of all red flags is not possible. Referral is needed any time a patient is in distress, whether that be psychological, respiratory, cardiovascular, etc. Another general principal is that signs and symptoms involving blood or bleeding are usually red flags. Any patient that you feel requires more treatment or assessment than you are competent to perform should be referred as well, whether it is to another pharmacist with different skills or to another healthcare provider. Examples of red flags identified during PA can include:

- *CNS*: Decreased LOC, acute confusion, delirium, sudden weakness, seizures, suicidal ideation, severe depression, signs or symptoms of mania, new gait disturbance
- *Eyes*: Vision changes, pain, feeling of foreign body, light sensitivity, double vision, exophthalmos, nystagmus, irregular pupils (fixed, large, or small)
- *Respiratory*: Dyspnea, difficulty breathing, abnormal findings on lung auscultation (e.g., wheeze, crackles, rhonchi, or stridor), worsened asthma or chronic obstructive pulmonary disease (COPD) symptoms, persistent cough
- *Cardiovascular*: Symptomatic or significant hypotension, marked hypertension, tachycardia or bradycardia, chest pain, arrhythmia or "palpitations," new or worsened heart failure symptoms, significant dehydration
- *MSK*: Distressing injury, poorly controlled rheumatoid arthritis, mobility issues, requirement for diagnostic imaging
- *GI*: Severe constipation, diarrhea, or vomiting, hematemesis, melena stools, bright red blood per rectum (BRBPR), pencil-like stools

- *GU*: Urinary tract infection symptoms, difficulty urinating, decreased urine output, hematuria
- *Infectious*: Signs or symptoms of sepsis, prolonged or high fever, flank pain or tenderness, suspected untreated infection
- *Dermatology*: Jaundice, cyanosis, signs and symptoms of anaphylaxis, rash with a fever especially in children

Case

The following case example demonstrates the use of physical assessment findings in patient assessment.

Patient JB is a 75-year-old male admitted to the medicine ward for acute exacerbation of COPD. He presented with accessory muscle use, hypoxia, and dyspnea. Today is postadmission day 3, and you are seeing JB for the first time on a Monday afternoon, as you missed seeing him on team rounds. Your team is gone for the afternoon, so you are seeing him by yourself. You decide to review JB closely as he seems unwell.

Chief complaint "I can't breathe very well."

History of present illness He has had COPD for 10 years and was only hospitalized once, 9 years ago. Currently uses fluticasone/salmeterol (Advair®) 500mg Diskus i puff bid, tiotropium (Spiriva®) Respimat ii puffs daily, and salbutamol (Ventolin®) ii puffs qid + prn (uses about 14 puffs per week). According to community pharmacy, Spiriva and Ventolin are filled regularly every 3 months, but Advair is filled sporadically, last filled 30-day supply 53 days ago.

PMHx HF (× 2 years), smoker (1 pack/day × 40 years), hypertension (× 10 years)

Current medications
Perindopril 8 mg po daily
Bisoprolol 5 mg po daily
Lasix 40mg iv bid (autostopped this morning because it was only ordered for 3 days)
Advair 500 mg Diskus i puff bid
Spiriva Respimat ii puffs daily
Ventolin ii puffs qid + prn
Atrovent ii puffs qid + prn
Prednisone 40mg po daily × 5 days

Vital signs (taken this morning) BP 110/80 mmHg, HR 70 bpm and regular, RR 25, O_2 saturation 90% on 4L, temperature 38.2 °C, GCS 15

Physical exam findings and review of systems (your own)
General survey: Patient is pleasant and appears at stated age; he is thin. Speech seems labored. He is alert and oriented x3 (to person, place and time). He is bed bound, and the head of the bed is elevated.
HEENT: Pupils equal, round, reactive to light, pursed lip breathing seen, no cyanosis observed
Dermatological: Not performed
Respiratory: Barrel chest, appears to be breathing hard, accessory muscle use visualized. Lungs have diffuse expiratory wheeze, rhonchi, and coarse crackles at the bases with dullness to percussion. Sputum is copious and green-colored.
Cardiovascular/peripheral vascular: Radial pulse regular, JVP 3cm, 2+ pitting edema to calves bilaterally
Abdomen: Not performed
GI/GU: Not performed
MSK: Not performed

History questions You complete a medication history and discover that JB ran out of his Advair at home as it was not covered by his insurance plan. His dyspnea is worse than baseline, he is producing more sputum than normal, and it has changed from yellow to green. No hemoptysis. He feels some dizziness and is short of breath. He also tells you that his shoes aren't fitting as well as they used to, and they feel tight. He reports sleeping with two pillows because he "coughs a lot when he just uses one."

Problem list and drug therapy problems are summarized in Table 3.9.

Table 3.9 Problem list and drug therapy problems for JB

Condition	Control/adherence	Drug therapy problems
AECOPD	Nonadherent to Advair because of cost Has signs of bacterial infection Multiple types of inhalers, assess technique	Reassessment of inhaler insurance coverage/ cost Additional therapy with antibiotics is needed
HF	Fine crackles at the bases present Pitting edema to calves Bisoprolol dose not optimized (10mg daily is target)	Requires continuation of diuretic therapy and reassessment of home dose Reassessment of route of diuretic (IV vs PO)
Dizziness	Blood pressure is 110/80, but do not have home values for comparison Assess for orthostasis	May require reassessment of antihypertensive therapy
Shortness of breath (SOB)	Could be due to any of: AECOPD, not using Advair, HF exacerbation	Need to clarify timeline when SOB worsened with patient

You decide to page the resident on call to discuss the drug therapy problems you have identified. Before calling, you prioritize the problems, and come up with specific suggestions including drug, dose, and route.

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Part II

Symptoms Assessment

Headache

4

Sherif Hanafy Mahmoud

Chapter Objectives

1. Describe the main types of headache disorders and their characteristics.
2. Assess patients presenting with headache.
3. Identify the red flags in patients presenting with headaches that prompt referral to health care practitioners or the emergency department.

Background

A patient comes to your pharmacy requesting something for his headache. What information do you need to conduct a proper assessment? To answer this question, pharmacists need to have a reasonable background about different types of headache disorders and how each type is being managed. In addition, gathering relevant patient-specific information spanning from symptom assessment to past medical history is essential to decide the proper course of action such as recommendation of an abortive therapy vs. referral.

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Headache is an ache in the head or, in other words, pain in the head. It is one of the most common symptoms encountered by healthcare practitioners. According to the international classification of headache disorders version III (ICHD-III), headache is divided into three distinct categories [1]. The first category is "primary headaches," which includes headaches not attributed to another disorder. Primary headaches are the most common types of headaches and include tension-type headaches (TTH), migraines, and cluster headaches. The second category is "secondary headaches." In this category, headache is essentially a symptom of an organic or psychiatric illness or induced by a substance (or drug) and/or its withdrawal. For proper assessment of patient's headaches, awareness of the possible causes of secondary headaches is essential. Secondary headaches range from an adverse reaction to a drug the patient is taking to a more serious life-threatening condition. The management of secondary headaches entails the management of the disease rather than the headache itself. For example, if a patient experiences headaches due to his uncontrolled hypertension, controlling the patient's blood pressure will potentially control the patient's headache. The third category is headache secondary to painful cranial neuropathies such as trigeminal neuralgia. Table 4.1 depicts a summary of the classification of headache disorders.

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Table 4.1 Classification of headache disorders

Primary headaches	Headaches not attributed to another disorder such as: Migraine Tension-type headache (TTH) Cluster headaches
Secondary headaches	Headache secondary to other disorders such as: Adverse reactions to drugs. Essentially any drug could cause headache. It is more important to confirm the temporal relation between drug initiation and symptom onset Medication overuse headache: rebound headaches due to the overuse of headache abortive therapies for more than 10–15 days per month Trauma Cerebrovascular causes, e.g., intracerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage Infection, e.g., common cold, flu Brain tumors Other organic illnesses, e.g., hypertension
Cranial neuropathies	Trigeminal neuralgia

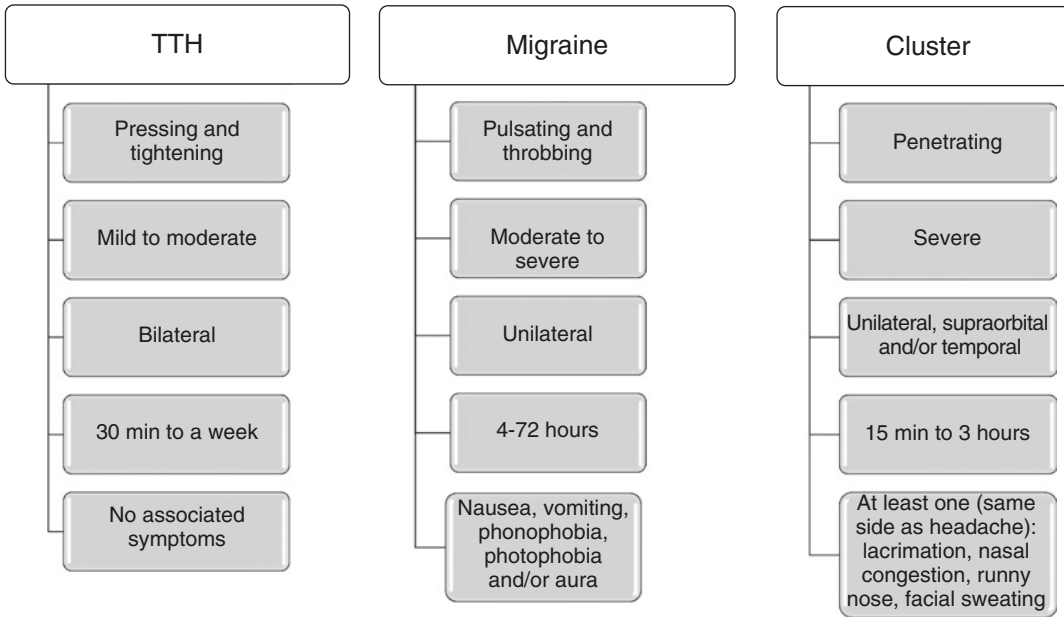


Fig. 4.1 Diagnostic criteria for the three main types of primary headaches: tension-type headache (TTH), migraine, and cluster headache

Primary Headaches

Figure 4.1 depicts the diagnostic criteria for the three main types of primary headaches: TTH, migraine, and cluster headache. TTH is the most common primary headache disorder. Most people experience it, with at least one attack in a lifetime. TTH may occur at any age but new onset is less common over the age of 50 years. It is usually mild to moderate in intensity and feels like there is a squeezing band around the head, dull, and non-pulsating. It is always felt by both sides of the head (bilateral) and rarely associated with other symptoms. A headache attack typically lasts from 20 minutes to up to 1 week. It is generally self-limiting and treated by over-the-

counter (OTC) analgesics such as acetaminophen and ibuprofen.

Migraine is the second most common primary headache disorder. The World Health Organization has considered migraine as one of the top 20 disabling illnesses worldwide. It is experienced by 15–20% of all females and 5–10% of all males with onset always below the age of 50 years. It is usually moderate to severe in intensity, throbbing and pulsating. It is usually felt by one side of the head (unilateral) and might be associated with nausea, vomiting, photo, and/or phonophobias. Migraine could be associated with or without aura. Auras are sensory perceptions that occur before the headache attack such as hearing sounds or seeing lights. A headache attack typically lasts from few hours to up to 3 days. It is generally treated with NSAIDs and triptans. Due to the severe disabling nature of the attacks, patients might benefit from prophylactic therapies such as propranolol and tricyclic antidepressants.

Cluster headaches are the most disabling type of primary headaches; fortunately, it is not as common as TTH or migraine. The overall incidence is 0.1% and is more common in males than females. It is characterized by very severe penetrating unilateral pain around the orbital area with associated autonomic symptoms such as lacrimation, sweating, and nasal congestion. A headache attack typically lasts from 15 minutes up to 3 hours. The short-lived nature of the headache attack makes conventional oral abortive therapies not practical or ineffective. By the time the drug is absorbed by the gastrointestinal tract, the headache attack could have been subsided.

Symptom Assessment (SCHOLAR)

To allow proper assessment of patients' headaches, the following information will need to be collected. If the patient was previously diagnosed with a headache disorder, a headache diary detailing the onset and severity of the attacks, preceding symptoms, aggravating factors, and medications taken with and without relief will be very helpful to assess the patient. Figure 4.2 depicts a flow chart describing assessment of patients presenting with headache in the pharmacy.

Symptoms

- In addition to your headache, did you experience any other symptoms?
- Did you experience any nausea or vomiting?
- Do you have any sensitivity to light or noise?

Clarifying the symptoms associated with the patient's headache will help in the differential diagnosis of the headache type (see Table 4.1 and Fig. 4.1) and identify the presence of any red flags.

Characteristics

- Please describe your headache. Is it throbbing, pulsating, or band-like?
- Was your recent headache different from the ones you experienced before?
- On a scale of 1–10, how severe is your headache?
- How often do you get these headaches?
- How long do your headaches last?

Clarifying the characteristics, severity, duration, and frequency of the attacks will help in the differential diagnosis of the headache type and identify the presence of any red flags.

History

- How long have you been having these headaches?
- Did this happen in the past? Was it different?
- Did you recently hit your head or had any injury?
- What were you doing when you got the headache attack?

Knowing the history of the patient's headache will help determine whether the headache occurs in an atypical pattern. In addition, above

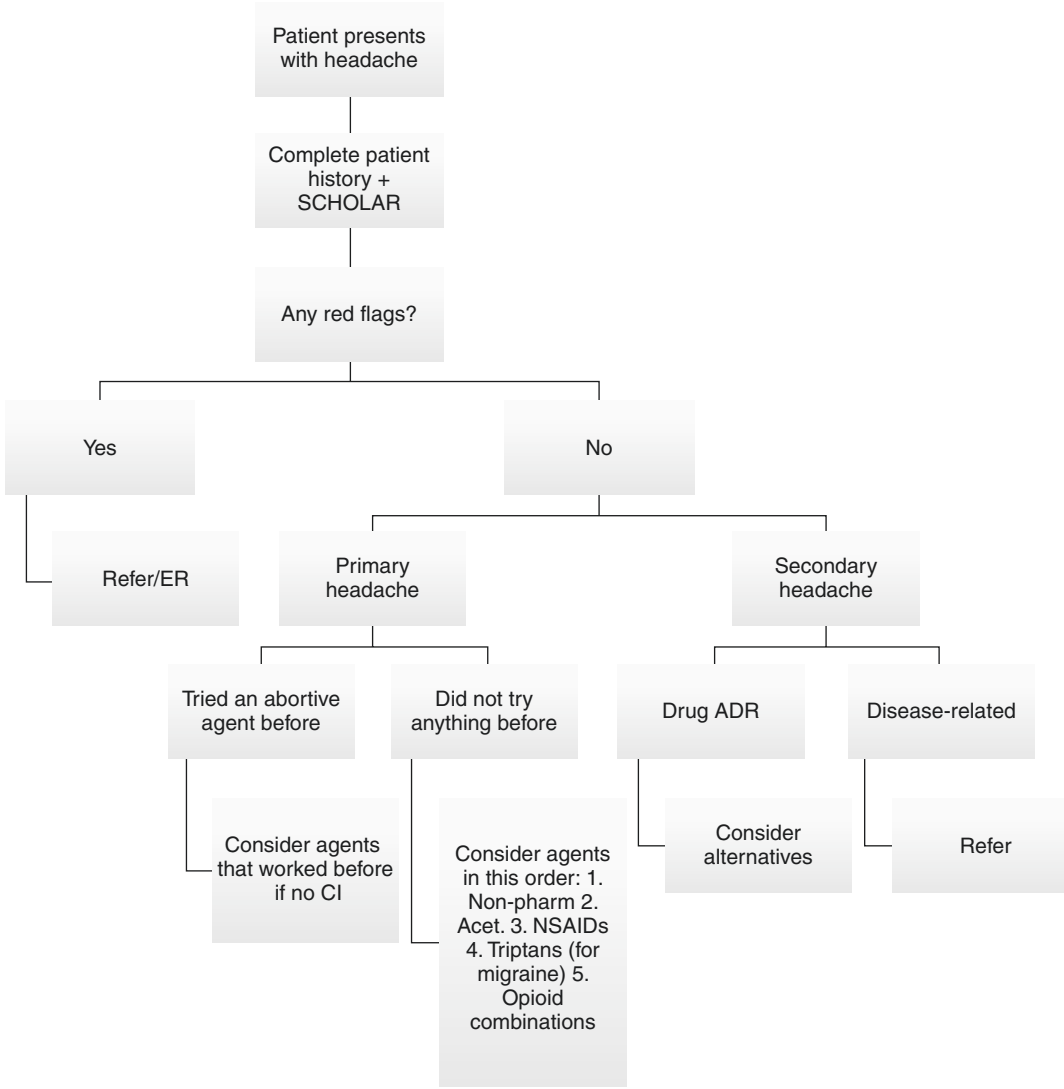


Fig. 4.2 Assessment of patients presenting with headache in the pharmacy. Acet., acetaminophen; ADR, adverse drug reactions; CI, contraindications; ER, emergency department; Non-pharm, nonpharmacological management; NSAIDs, nonsteroidal anti-inflammatory drugs; SCHOLAR, **S**ymptoms, **C**haracteristics, **H**istory, **O**nset, **L**ocation, **A**ggravating and **R**emitting factors

questions will help identify any triggers or external precipitants.

Onset

- Was this your first headache attack?
- When did your headaches start?
- Was your headache gradual or abrupt?

Clarifying the age at onset and temporal evolution of the patient's headache will help in the identification of the presence of any red flags.

Location

- Describe the location of your headache. Is it unilateral or bilateral?

Clarifying the location of the patient's headache will help in the differential diagnosis of the headache type (see Fig. 4.1).

Aggravating Factors

- What makes your headache worse? A discussion about patient's triggers.

Although primary headaches are not attributed to a certain cause, there are factors that could precipitate or aggravate the attacks. To illustrate, TTH and migraine could be precipitated by mental stress, smoking, fatigue, lack of sleep, weather changes, and prolonged poor body posture associated with excessive use of computers. In addition, some kinds of food might precipitate a headache attack in certain individuals such as tyramine containing food and chocolate. Furthermore, headaches might be associated with menses and oral contraceptive use in some patients. Fasting and caffeine intake abstention in coffee drinkers could also precipitate headache in some individuals. With regard to cluster headache, vasodilators and alcohol intake could precipitate or aggravate cluster attacks. Identification of those triggers will aid in tailoring the nonpharmacological management. For example, maintaining adequate sleep could help with headaches aggravated by lack of sleep. In addition to avoiding triggers, other nonpharmacological measures include biofeedback and relaxation therapy.

Remitting Factors

- What makes your headache better? Pharmacological and nonpharmacological.
- What did not work for you?
- Was the medication effective in aborting the headache attack completely?
- Was there any side effects from the medications you took to relief your headache attack?

Various treatment options are available for headache disorders [2, 3]. Table 4.2 summarizes the abortive agents used in controlling primary headache disorders. It is necessary to check the patient's previous experience with abortive agents. What worked for the patient before might work for him again and vice versa. In addition, if the patient experienced an adverse or allergic reaction from the drug before, alternative options might need to be considered. To illustrate, if acetaminophen did not work for a patient recently diagnosed with migraine, he might try any of the over the counter NSAIDs given that they are not contraindicated. In addition to checking medication efficacy, the dose taken needs to be checked. Some patients might be under- or overdosing their medications and this might affect assessment. For example, sumatriptan recommended oral dosage range is 25–100 mg/dose with maximum 200 mg/day. A dose of 25 mg is less likely to be effective than 50 mg. On the other hand, a 100 mg dose is more likely to be effective but at the same time, it is more likely for the patient to experience adverse reactions. If the patient tried a

Table 4.2 Abortive agents used in controlling primary headaches

Headache type	Abortive agents (suggested oral dose)
Tension-type headache	Acetaminophen (325–1000 mg, max 4 g per day) with or without codeine (8–30 mg) NSAIDs, e.g., ibuprofen (200–400 mg) and naproxen (250–500 mg)
Migraine	Acetaminophen (325–1000 mg) with or without codeine (8–30 mg) NSAIDs Triptans: Sumatriptan (oral, 25–100 mg, max 200 mg/day; subcutaneous 6 mg, max 12 mg/day; nasal solution 5–20 mg, max 40 mg/day) Naratriptan (1–2.5 mg, max 5 mg/day) Almotriptan (6.5–12.5 mg, max 25 mg/day) Eletriptan (20–40 mg, max 40 mg/day) Frovatriptan (2.5 mg, max 5 mg/day) Zolmitriptan (oral and nasal spray 2.5 mg, max 5 mg/day) Rizatriptan (5–10 mg, max 20 mg/day) Triptans + NSAIDs Ergot derivatives
Cluster headache	Inhaled oxygen Subcutaneous sumatriptan

NSAIDs nonsteroidal anti-inflammatory drugs

Table 4.3 Prophylactic drug treatment strategies for migraine based on the clinical setting[a]

Prophylaxis strategy	Suggested agents
First-time strategy	Beta blockers: propranolol, nadolol, metoprolol Tricyclic antidepressants: amitriptyline, nortriptyline
Low side effect strategy	Drug: candesartan, lisinopril Herbal / vitamin / mineral: magnesium citrate, riboflavin, butterbur, Coenzyme Q10
Increased body mass index strategy	Topiramate
Hypertension strategy	Propranolol, nadolol, metoprolol, candesartan, lisinopril
Depression/anxiety strategy	amitriptyline, venlafaxine, nortriptyline
Additional monotherapy drug strategy	Topiramate, divalproex, gabapentin, pizotifen, flunarizine, verapamil
Refractory patient strategy	Concomitant use of two drugs
Migraine during pregnancy strategy	Drug avoidance if possible If necessary, magnesium, propranolol, metoprolol, amitriptyline, and nortriptyline
Migraine during lactation strategy	Drug avoidance if possible. When necessary, magnesium, propranolol, nadolol, metoprolol, amitriptyline, nortriptyline, and valproate

[a]From Pringsheim et al. [4], reproduced with permission

25 mg dose and it did not work for him, he might try a 50 mg dose. Conversely, if he tried a 100 mg dose and it did not work for him, sumatriptan is likely ineffective and alternative agents need to be tried.

- How often do you take the headache medications?

It is important to ask about the frequency of abortive agents' administration. This will determine if the patient is at risk of or actually experiencing medication overuse headache (MOH). Generally, MOH is defined as the recurrence of headache attacks for more than 15 days per month which get worse with administration of abortive agents [1]. Patients at risk are those who use triptans, opioids, opioid combinations, and barbiturates for more than 10 days per month or those who use acetaminophen or NSAIDs for more than 15 days per month. Those patients could benefit from prophylactic therapies.

- Are you on any medication to prevent further headache attacks? If yes, what is the dose and for how long have you been on it?

Patients diagnosed with primary headaches that are severe enough to limit their daily activities, those who experience frequent headaches, and/or those where most of the abortive agents are not effective or contraindicated might benefit from headache prophylaxis. Due to the severity of migraine and cluster headaches, prophylactic therapies are common in these conditions. Patients on prophylactic therapies need to be assessed for the appropriateness of the agent used in light of the patient's comorbidities, efficacy, and safety. The Canadian headache society guidelines for migraine prophylaxis has provided prophylactic agent selection suggestions based on the clinical setting and patient comorbidities (Table 4.3) [4]. These suggestions could be helpful while assessing patients on or need prophylactic therapies. With regard to efficacy, it generally takes several weeks for the agent to provide a benefit. If the prophylactic agent has failed, with adequate trial at target dose for 2 months, a trial of another or additional agent is recommended.

Patient-Specific Characteristics

In addition to assessing the patient's symptoms, a knowledge of the patient's medical and medication history allows proper selection and/or assessment of the appropriate abortive agent. The following examples illustrate how patient-

specific characteristics are essential in headache assessment:

- *Age:* The age of the patient at headache onset is important to determine if there is any red flag. New-onset headache at ages older than 50 or younger than 5 years is considered a red flag and prompts referral to a health care professional for further assessment.
- *Pregnancy status:* Nonpharmacological measures and acetaminophen are the abortive agents of choice in pregnant women.
- *Past medical history:* Identifying patient's comorbidities will help in recognizing the possible causes of secondary headaches and the presence of any comorbidities that contraindicates the use of specific abortive agents. For example, a history of peptic ulcer disease precludes the use of NSAIDs and a history of ischemic heart disease precludes the use of triptans and ergot derivatives. Table 4.4 summarizes the precautions and contraindications of commonly used headache abortive agents. Another example, a patient with a history of hypertension could prompt the pharmacist to assess the patient's blood pressure control as a potential cause to the patient's headache.
- *Medication history:* Identifying patient's current medications will help recognize the possibility of drug-induced headaches or any possible drug interaction with the abortive agents. Essentially, any drug could cause headache. It is more important to confirm the temporal relation between drug initiation and symptom onset. In addition, it is recommended that pharmacists to always check for the presence of any clinically significant drug interactions when assessing their patients.

Red Flags

It is very important to determine if the patient's headache could be caused by an underlying medical condition, which could be, in some occasions,

Table 4.4 Precautions and contraindications of commonly used abortive agents

Abortive agent	Precautions and contraindications that pharmacists need to be aware of when assessing patients with headache
Acetaminophen	Precautions Maximum dose is 4 g per day from all products containing acetaminophen to avoid hepatotoxicity Heavy alcohol use Patients with liver disease Contraindications Allergy to acetaminophen Avoid in patients with severe active liver disease
NSAIDs	Precautions Risk for or presence of cardiovascular disease History of gastrointestinal bleeding and peptic ulcer disease Patients at risk of hyperkalemia Liver impairment Asthma (contraindicated in aspirin-sensitive asthma) Contraindication Allergy to NSAIDs or ASA Active bleeding Active gastrointestinal bleeding and peptic ulcer disease Renal impairment
Triptans	Precautions Poorly controlled hypertension Smoking Pregnancy and breastfeeding Contraindications Ischemic heart diseases Cerebrovascular diseases such as previous stroke Peripheral vascular diseases

NSAIDs nonsteroidal anti-inflammatory drugs

life-threatening. Presence of any of the following red flags prompts referral to a health care practitioner or the emergency department:

- *New-onset headache at ages older than 50 years*: New-onset headache at age older than 50 years should prompt the pharmacist to refer the patient to the physician or a specialist for further assessment as this could be potentially caused by an organic illness or a space occupying lesion such as brain tumors.
- *New-onset headache in immunosuppressed individuals*: New-onset headache in immunocompromised patients could be caused by central nervous system infections such as meningitis or brain abscess and should be ruled out.
- *New-onset severe headache in pregnant women*: Severe headache during pregnancy needs referral to rule out eclampsia or cerebral venous sinus thrombosis.
- *New-onset severe and abrupt "thunderclap" headache*: Acute-onset severe headache could be caused by potentially life-threatening conditions such as subarachnoid hemorrhage, intracerebral hemorrhage, meningitis, or presence of mass-occupying lesion. It is strongly recommended that the patient should seek immediate medical attention and go to the emergency department to be examined. For example, many patients with subarachnoid hemorrhage, a life-threatening brain bleed, present with severe thunderclap headache as the only symptom.
- *Increased frequency or increased severity of headaches*: Progressive headache symptoms could indicate space-occupying lesions such as brain tumors, brain abscesses, and chronic subdural hematomas (seen in patients on anticoagulants and those with recent trauma to the head). Furthermore, progressive headaches could indicate medication overuse headache. This needs to be assessed through identifying the number of abortive therapies the patient is taking per month. Ruling out secondary causes of headache in patients with MOH is essential.
- *Headache in patients with recent head trauma.*
- *Significant change in the pattern of the headaches the patient is getting*: Changes in headache pattern could indicate a more serious condition and should be closely examined.
- *Presence of other symptoms* that indicate a more serious cause of the patient's headache such as stiff neck, altered level of consciousness, fever, motor weakness, and other focal neurological symptoms prompts referral.

Additional Assessment Considerations

Since primary headaches are not attributable to any underlying etiology, normal physical examination is expected. However, if secondary causes are expected, further investigations are warranted. Examples of further investigations include imaging such as head computed tomography (CT scans), CT angiography, and magnetic resonance imaging (MRI scans). In addition, lumbar puncture, dental examination, and endocrine, biochemical, infection, and oncological workup are recommended.

Follow-up assessment is recommended for patients with headache. Pharmacists should advise patients especially the ones with frequent headaches to maintain a headache diary detailing their episodes, possible precipitating and ameliorating factors. In addition, headache severity and frequency, the dose of the abortive agent, response to therapy, presence of any adverse reactions need to be noted in the headache diary.

Clinical Pearls

- Pharmacists play an important role in identifying red flags in patients presenting with headaches.
- Assessment of patients presenting with headaches involve the following two key steps:
  (a) Assessment of the characteristics and history of patients' headaches and the presence of any associated symptoms.
  (b) Assessment of the appropriateness of the abortive and prophylactic agents, when applicable.
- Pharmacists need to assess for medication overuse headache in patients frequently taking abortive agents for their headaches.

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Cough

5

Elizabeth Glashan and Sherif Hanafy Mahmoud

Chapter Objectives

1. Outline common etiologies of cough.
2. Assess patients with cough.
3. Identify patients who may benefit from symptomatic therapy for cough.
4. Identify red flag symptoms that indicate need for referral and urgent assessment.

Background

Cough is a very common symptom that results in around 30 million healthcare visits each year in the USA [1]. Severity ranges from mild, all the way to severe excessive cough which can cause vomiting, urinary incontinence, and even rib fractures. The cough reflex serves a purpose, and that is to clear the airway from bacteria, debris, and secretions. The physiologic pathway that results in cough is rather complex. Humans have cough receptors in the respiratory tract, pericardium, diaphragm, pleura, esophagus, and stomach. There are chemical and mechanical receptors that respond to a variety of stimuli which results in an impulse that travels through the vagus nerve to the "cough centre" in the medulla. An efferent signal then travels down to the spinal motor nerves to the expiratory musculature, producing cough [2]. Despite serving a purpose physiologically, cough is an unpleasant symptom and proves to be the most common new complaint seen in primary care [3]. There are many possible causes for a troublesome cough. The American College of Chest Physicians (ACCP) suggests that assessing the duration of symptoms is the most useful first step in assessing patients who present with cough. Based on duration, cough is classified as acute (<3 weeks), subacute (3–8 weeks), and chronic (>8 weeks). Duration of symptoms is key because acute, subacute, and chronic cough each has distinct etiologies [4]. Generally, patients with cough >3 weeks should be referred to their physician. Pharmacists play an important role in the assessment and management of patients with cough. They can identify patients who need urgent medical attention, those who are appropriate for self-care, and anyone in between. Cough assessment involves gathering a focused history from the patient, concentrating on clinical features, exposure history, presence or absence of red flags, and key patient-specific factors. Once the pharmacist has gathered the necessary information, he/she can move on to next steps such as prescribing an OTC medication or referral to the family physician or the emergency department.

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Etiology

Acute cough is most commonly caused by viral infections, followed by exacerbations of asthma or chronic obstructive pulmonary disease (COPD), or pneumonia. Other conditions to consider, depending on symptomatology, include pulmonary embolism (PE), or heart failure (HF). Tuberculosis (TB) should be considered in endemic areas, or high-risk populations, regardless of symptom duration [4]. Similarly, *subacute cough* is commonly postinfectious or secondary to asthma or COPD exacerbations. Upper airway cough syndrome (UACS) is another common cause of subacute cough (see below) [4]. *Chronic cough* is most commonly caused by UACS, asthma, GERD, or nonasthmatic eosinophilic bronchitis (NAEB). Furthermore, medications can be associated with acute, subacute, and chronic cough. Based on that, the main etiologies of cough can be grouped into the following categories: infectious, disease-related, and medication-related cough.

Infectious Cough

Upper Respiratory Tract Infection

Upper respiratory tract infections (URTI) are most commonly caused by viral pathogens and often present as the "common cold." Symptoms include acute cough, rhinorrhea, sneezing, sore throat, mild fever, malaise, and headache. Cough often lingers after the other symptoms have resolved. This is called a postinfectious cough and is a common cause of subacute cough. Postinfectious cough is thought to be caused by a combination of postnasal drip and a direct sensitizing effect of the virus on airway receptors [5]. Both of these mechanisms fall under the umbrella of upper airway cough syndrome (UACS), which is discussed in the disease-related cough section. Table 5.1 shows the infectious syndromes that cause cough.

Table 5.1 Infectious causes of cough

Syndrome	Organisms
URTI ("common cold")	Rhinovirus Coronavirus Parainfluenza virus Respiratory syncytial virus
Influenza	Influenza A or B
Acute bronchitis	Viruses cause ≥90% of cases, see above pathogens
Pneumonia	Viruses (URTI organisms and influenza) Bacteria (community acquired pneumonia): *Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella cattarhalis* Atypical organisms: *Mycoplasma pneumoniae* *Chlamydophila pnemoniae* *Legionella* spp
Tuberculosis	*Mycobacterium tuberculosis*
Whooping cough	*Bordetella pertussis*

URTI upper respiratory tract infection

Pneumonia

Pneumonia is a common cause of acute cough. It is an infection of the pulmonary parenchyma, and has the potential to cause severe illness and death. Symptoms of pneumonia include productive cough, fever, malaise, fatigue, pleuritic chest pain, and dyspnea. If pneumonia is suspected, referral is required for further work-up and treatment [6]. "Atypical" organisms (see Table 5.1) can cause a different constellation of symptoms. They may present with acute or persistent cough, either productive or nonproductive [7].

Influenza

Influenza is an important viral pathogen that causes outbreaks in a seasonal pattern, usually peaking in winter months. It is commonly spread through droplet transmission. Main symptoms include cough, fever, myalgia, rhinorrhea, headache, and fatigue. Influenza is usually self-limited in previously healthy individuals. Despite this, certain strains can cause high rates of morbidity and mortality among young adults and children. The 2009 pandemic H1N1 is an example of this [8]. Usual risk factors for complications from influenza are:

- Age >65 years old
- Nursing home residence

- Pregnancy
- Chronic medical conditions such as asthma, COPD, diabetes mellitus (DM), cardiovascular disease, immunosuppression, or obesity

Complications include pneumonia, hospitalization, and worsening of preexisting conditions. An estimated 300,000 to 640,000 influenza-related deaths occur each year worldwide. Diligent hand hygiene and annual vaccination are the best safeguards against influenza [8, 9].

Tuberculosis

Tuberculosis (TB) is caused by the bacteria *Mycoplasma tuberculosis*. Around 90% of people who get infected never develop the disease and instead have what is called latent TB infection (LTBI). Five percent of people with LTBI do develop active TB when it becomes reactivated, and 5% of people who get infected do develop active TB within 18 to 24 months of infection. Active TB most commonly affects the lungs but can also infect the brain, kidney, and bones. Productive chronic cough with or without hemoptysis is one of the common symptoms of active TB. Persistent fever, weight loss, night sweats, chest pain, and fatigue are other common symptoms [10–12]. Risk factors for acquiring TB include:

- Homelessness, incarceration, or illicit drug use
- Immunosuppression, chronic kidney disease on hemodialysis (CKD-HD), or diabetes mellitus (DM)
- Residence or travel to an area with high rates of TB [10]. In Canada, this includes First Nations reserve communities [11]

Any patient with a cough lasting longer than 2–3 weeks should be referred and investigated for TB if they have any additional TB symptoms [12].

Pertussis ("Whooping Cough")

Pertussis, also known as "whooping cough," is caused by the bacteria *Bordetella pertussis*. It is a highly contagious and underdiagnosed condition. Cough is one of the most common symptoms, and it can last up to 8 weeks. This cough is generally severe hacking, associated with vomiting after a coughing fit, and sometimes presents with a whooping sound. Any patient with cough lasting more than 2–3 weeks should be referred, and pertussis, among other things, should be ruled out [13].

Disease-Related Cough

Asthma

Asthma exacerbation can present with acute cough, as well as wheezing, breathlessness, and chest tightness. Inflammation, bronchospasm, and excess mucous trigger these symptoms [14]. Severe asthma exacerbations can be life-threatening, and can occur in patients with any baseline level of severity. Patients at high risk for asthma-related death include those who [15]:

- Have had a previous severe exacerbation
- Use >2 canisters of salbutamol (or other short-acting beta agonist [SABA]) per month
- Had ≥2 hospitalizations or ≥3 ER visits in the past year
- Are unable to recognize airway obstruction or severity of worsening asthma
- Are of lower socioeconomic status, or residence in inner city
- Use illicit drugs or have psychiatric illness or psychosocial problems
- Have medical comorbidities such as cardiovascular disease or other lung disease

For patients who are not at high risk for fatal exacerbation, mild exacerbations can be managed at home, as long as they respond to initial therapy (e.g., 2–6 puffs of salbutamol every 20 minutes when necessary). After initial therapy, patients should contact their physician for further management such as consideration for oral corticosteroids. For more severe exacerbations (marked breathlessness, impaired speech, accessory muscle use, or drowsiness), patients should use initial therapy with salbutamol as above and proceed to the ER urgently for assessment and management. Peak expiratory flow (PEF) is a valuable parameter for monitoring in asthmatics, both acutely in

exacerbations and chronically for assessing long-term control. Of note, chronic cough is also common in asthma. Cough and other symptoms are often worse at night and early morning. For an asthmatic patient with worsening symptoms such as chronic cough, breathlessness, declining PEF readings, or increased use of rescue medication, a lack of control exists. Their preventive medication regimen should be reevaluated and likely stepped up. These patients should be referred to their family physician or specialist in a timely manner [15].

Chronic Obstructive Pulmonary Disease

Acute exacerbation of COPD (AECOPD) is defined as a change in respiratory status that exceeds normal day-to-day variations and requires additional therapy. AECOPD is marked by three cardinal symptoms: worsened dyspnea, increased sputum production, and increased sputum purulence [16]. More than 80% of exacerbations can be managed in the outpatient setting, with intensified bronchodilators, prednisone, with or without antibiotics [16]. Patients with AECOPD need to be referred. Patients who might need ventilatory support (e.g., hypoxia, resting dyspnea, RR > 20–30, cyanosis, increased work of breathing) or those who cannot manage their symptoms at home [16] should be referred to their physician or to the emergency department.

Heart Failure

Acute decompensated heart failure (ADHF) is another cause of acute cough. All patients with ADHF should be referred to either their physician or to the ER, depending on the severity of symptoms. Many patients will require hospitalization, including those with dyspnea at rest, hypotension, altered mentation, >2 kg weight gain, or worsened peripheral edema. In-hospital mortality for high-risk patients is up to 22% [17]. Severe pulmonary edema can cause a productive cough with frothy pink liquid sputum. Other symptoms of acute or chronic heart failure include fatigue, weakness, nausea, decreased appetite, shortness of breath, and reduced exercise tolerance. Cough can be a chronic symptom of heart failure and is often worse at night, as it is due to fluid overload.

Pulmonary Embolism

PE is an important consideration in patients with acute cough [4]. PE can cause significant morbidity and mortality, especially when left untreated. Virchow's triad represents three broad categories of risk for thrombosis: endothelial injury, blood flow stasis, and hypercoagulability. Recent deep vein thrombosis (DVT), trauma, surgery, immobility, and current diagnosis of cancer are examples of risk factors for PE. Patients with PE often present with dyspnea, pleuritic chest pain, and cough, sometimes with hemoptysis. Any patients with acute cough who may be at risk for PE should be referred to the ER for prompt assessment [4].

Upper Airway Cough Syndrome

Upper airway cough syndrome (UACS) is the most common cause of chronic cough. It was previously known as postnasal drip. ACCP renamed it UACS to include etiologies with postnasal drip, as well as irritation of cough receptors in the upper airway. UACS is caused by a heterogeneous group of rhinosinusitis illnesses, including allergic rhinitis, vasomotor rhinitis, and sinusitis. UACS is usually diagnosed after sequential empiric therapies are tried, such as first-generation antihistamines or decongestants. Referral to primary care provider is required [18].

GERD

GERD is one of the most common causes of chronic cough, causing up to 30–40% of cases. Many of these patients experience dyspepsia, heartburn, or a sour taste. However, up to 40% of patients with cough due to reflux do not have any traditional GERD symptoms. It is thought that refluxed acid and stomach contents stimulate receptors in the upper and lower respiratory tract, leading to cough [19]. ACCP recommends empiric antireflux therapy for patients who have chronic cough and classic symptoms of GERD. If there is no other explanation for the cough after evaluation, a trial of antireflux therapy is also recommended for patients with chronic cough even if they do not have GERD symptoms [1]. Antireflux therapy should include lifestyle modification (weight loss if overweight, limiting fat intake, smoking cessation, etc.) as well as pro-

ton pump inhibitor use. Further options include metoclopramide and antireflux surgery [20].

Other diseases associated with chronic cough include nonasthmatic eosinophilic bronchitis, also known as cough-variant asthma. All patients with subacute or chronic cough should be referred to their primary care provider, specialist, or urgent care, as appropriate, since chronic illnesses are frequently the cause.

Medication-Related Cough

Cough is listed as a possible adverse effect for countless medications. In order to assess whether cough could be due to a medication, one must consider the temporal relationship between initiation of the medication and cough. Observed frequency of cough associated with the medication or class of medications provides another important clue. Table 5.2 lists drugs that have been associated with cough [21].

Table 5.2 Medications that have been associated with cough [21]

Medication groups associated with cough	ACE inhibitors Antiretrovirals Antifungals Beta-blockers Chemotherapy agents Inhaled medications Immunosuppressants Liposomal drug formulations Monoclonal antibodies (-“mab”) Recombinant DNA drugs (e.g., eltrombopag, filgrastim, erythrocyte stimulating agents, insulin glargine, dornase alfa) NSAIDs Tyrosine kinase inhibitors (“-inib”)
Individual drugs associated with cough >10%	Atovaquone Cinacalcet Desloratadine Glutamine Immune globulin Nicotine Octreotide Pamidronate Sacubitril and valsartan (9%)

ACE angiotensin-converting enzyme, *DNA* deoxyribonucleic acid, *NSAIDs* nonsteroidal anti-inflammatory drug

Angiotensin-Converting Enzyme (ACE) Inhibitor-Induced Cough

ACE inhibitors are one of the most commonly implicated medications for drug-induced cough. It has been described as a persistent dry cough, sometimes with a scratching or tingling sensation in the throat [22]. The incidence is anywhere from 5% to 35% of patients taking this class of medication. The exact mechanism of this adverse effect is unknown. Bradykinin and substance P likely play a role. These molecules are normally broken down by ACE, and thus build up in the presence of an ACE inhibitor. It has been proposed that bradykinin sensitizes airway sensory nerves, possibly through increasing prostaglandin levels [22, 23]. Onset of ACE inhibitor-induced cough ranges from hours to months after initiation of therapy. After stopping the ACE inhibitor, resolution of cough usually occurs within 1–4 weeks but may take up to 3 or more months. Cessation of ACE inhibitor is recommended for all patients with chronic cough who are taking an ACE inhibitor [22]. Upon rechallenge, cough will recur in approximately 67% of patients. Rechallenge may be reasonable in patients with compelling indication for ACE inhibitor therapy [24]. Most patients can be switched to an angiotensin II receptor blocker (ARB), as these agents have proven efficacy for many of the same indications, and are much less likely to cause cough [22].

Symptom Assessment (SCHOLAR)

Patient assessment using the SCHOLAR approach provides a systematic framework to elicit necessary information, clarify the differential diagnosis, and identify red flag features. Figure 5.1 depicts the initial assessment and general management approach to cough. The following questions are suggested in order to assess patients presenting with cough.

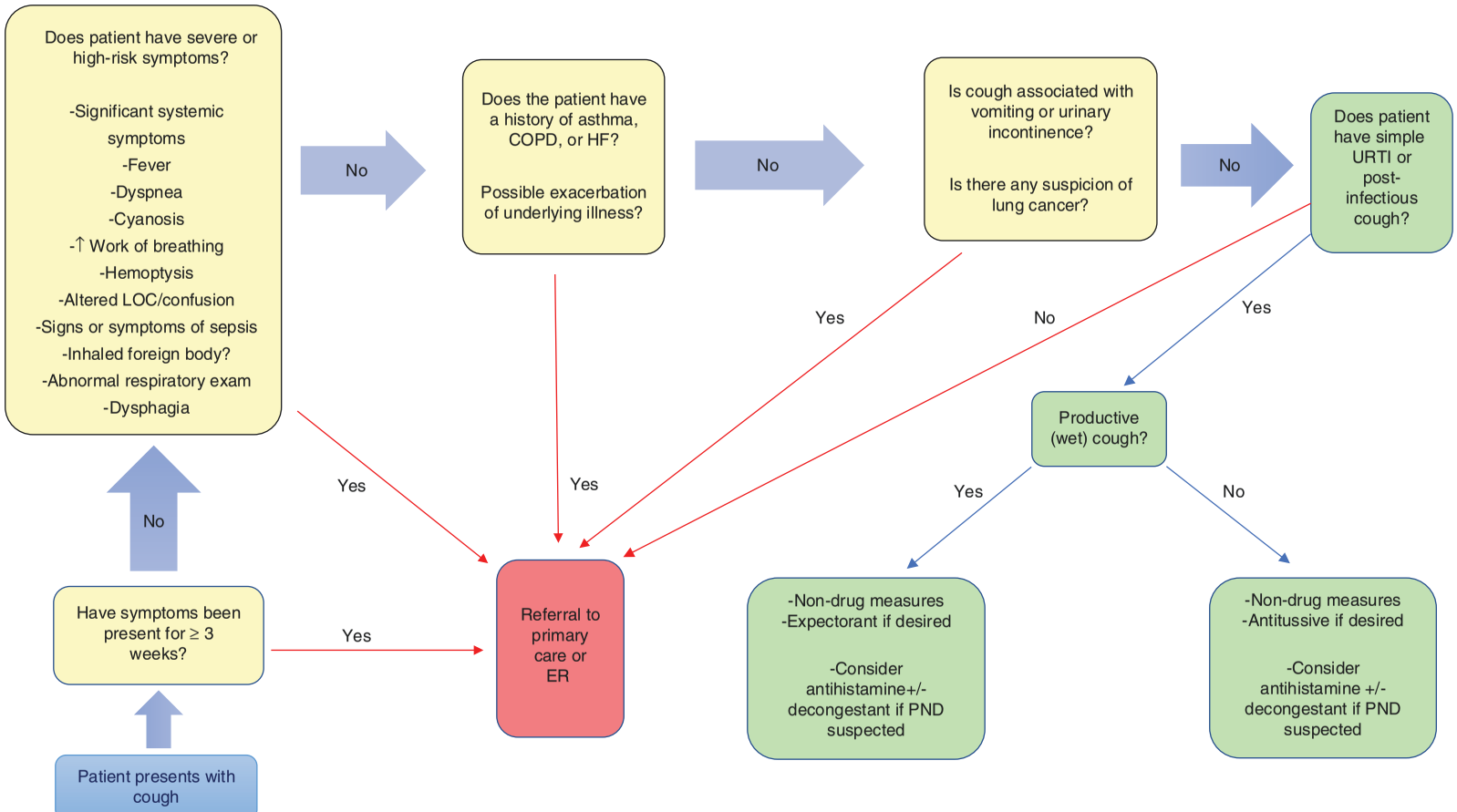


Fig. 5.1 Initial assessment and general management approach to cough. COPD, chronic obstructive pulmonary disease; HF, heart failure; LOC, level of consciousness; PND, postnasal drip; URTI, upper respiratory tract infection

Symptoms (Main and Associated)

- Please describe your symptoms.
- Are you producing any sputum? How much sputum comes up?
- Have you experienced urinary incontinence associated with your cough?
- Have you experienced vomiting due to your cough?
- Do you have any sharp chest pain associated with your cough?
- Do you have a fever or chills?
- Do you have sore muscles (myalgias)?
- Do you feel weak or tired?
- Do you feel short of breath? Are you limited in the amount or intensity of physical exertion you can perform?
- Have you noticed any wheezing?
- For asthmatics (if they monitor PEF): has your PEF declined from baseline?
- Do you have heartburn symptoms?
- Has your voice become hoarse?
- Have you noticed any swelling in your legs or feet? Have you gained weight?
- Do you have any difficulties or pain with swallowing?

It is essential to ascertain the main and associated symptoms. It is also critical to know whether the cough is productive or not, as this will guide therapy if the patient is asking for a cough medication. Further questions identify red flags (see "Red Flags" section). If the cough is severe enough to cause vomiting, this may be a case of pertussis and referral is required. Additionally, cough severe enough to cause urinary incontinence requires primary care referral. These questions will also help identify patients with asthma exacerbation.

Characteristics

- Is it a dry hacking cough?
- If you do have sputum, what does it look like? What color is it? Is there blood in it? Is it pink and frothy?
- For patients with COPD: Have you noticed an increase in the amount of sputum production? Has your sputum changed color or consistency?

The characteristics questions further identify patients who need to be referred (see "Red Flags" section).

History

- Have you had a similar illness like this before?
- Do you smoke cigarettes, cigars, pipes, or any other products?
- What is your past medical history? The following conditions are particularly relevant to cough: COPD, asthma, HF, history of allergies, history of DVT or PE, and history of cancer.
- What medications do you take?
- Have you recently started taking any new medications?
- Have you recently moved from or traveled to an area where TB is endemic (see [10] and [11])?
- Have you had any recent sick contacts at school, work, or at home?

History questions will elicit important information about medical history, and medications, including any potential for medication-induced cough. Each of these helps identify what the etiology of the cough is, as well as management options. If sick contacts are identified, this can help identify the cause of cough as well. For example, if there is a "cold" going around at school, and the symptoms are consistent with this, the patient very likely has a viral URTI. Anyone with cough who has risk factors for, or additional symptoms of, TB should be referred for evaluation [4].

Onset

- How long have you had your cough?
- Is your cough worse at night?

The duration of symptoms is a key piece of information that helps narrow the differential diagnosis greatly. A cough that is worse at night could be due to certain causes (e.g., asthma or HF).

Location

- If the patient has chest pain, explore its location.

Aggravating Factors

- Can you think of anything that makes your cough worse?
- Does exercise or cold air make it worse?
- Does laughing or talking make it worse?
- Does laying down make it worse?
- Are you exposed to noxious chemicals at your job?
- Have you noticed any environmental triggers?
- Do you have any allergies?

Identifying triggers can help the patient to avoid them, if possible. This can also help identify the etiology of the cough, and whether the patient requires referral.

Remitting Factors (Treatment Options)

- Have you tried any pharmacologic or nonpharmacologic remedies? Has anything helped? Did anything not help?
- Did you experience any side effects?

Nonpharmacological Measures

Humidifying the air and staying hydrated may provide relief for some individuals. Honey, either on its own or mixed with hot water and lemon, is a strategy that may provide some soothing relief as well. Smoking cessation is a great option for anyone who is ready and willing to try a quit attempt. Many people actually experience an increase in sputum production in the first few days of a quit attempt, but they should be reassured that this is temporary and that cough will be greatly reduced in the long run by smoking cessation. For patients with allergies or sensitivities, avoiding triggers can make a big difference for cough and associated symptoms. This often involves a trial-and-error approach. Hand hygiene and covering ones mouth when coughing are extremely important strategies for preventing the spread of infection.

Pharmacological Measures

Cough can be quite a nuisance during the daytime, and can definitely interfere with sleep as well. Many patients may wish to try medication to alleviate their symptoms. It is important to distinguish a productive ("wet") cough from a nonproductive ("dry") cough. For patients with a productive cough, antitussive medications should be avoided, as they can prolong and worsen their illness [25]. For these patients, an expectorant such as guaifenesin can be tried, which has a mechanism of action of loosening phlegm and helping to expel it. For patients with a nonproductive cough, an antitussive such as dextromethorphan can help lessen their coughing. Table 5.3 depicts the pharmacologic options for cough in adults. Cough and cold medications are not appropriate for over-the-counter use in children <6 years old, as per Health Canada guidelines. Serious adverse effects have occurred in young children. This warning includes first-generation antihistamines, antitussives, expectorants, and decongestants. Use of these medications in children must be in conjunction with a primary care provider [26]. For bacterial infections, such as community-acquired pneumonia, antibiotics will likely be required. Choice of antibiotics depends on severity of illness, previous antibiotic exposure, etc. and is beyond the scope of this chapter. For patients with influenza, oseltamivir should be considered if symptom duration is <48 hours or for those at risk of complications from influenza. Oseltamivir may decrease symptom duration by 12 to 72 hours [27]. The seasonal influenza vaccine should also be given to most people for prevention of influenza.

Red Flags

Red flags signal a need for referral to another healthcare practitioner or the emergency room in some cases. Pharmacists play a key role in identifying patients who have red flag features.

- Cough ≥3-week duration

Table 5.3 Pharmacologic options for cough in adults [18, 19]

Drug	Dose	Comments
Dextromethorphan	10–20 mg by mouth every 4 hours as needed	Antitussive, not recommended for use in productive cough Structurally related to codeine CYP 2D6 metabolism (genetic polymorphisms common) Screen for drug interactions (may precipitate serotonin syndrome)
Codeine	10–20 mg by mouth every 4 hours as needed	Antitussive, not recommended for use in productive cough Not safe in pediatric population due to CYP 2D6 polymorphisms and potential for supratherapeutic levels in fast metabolizers. Deaths have occurred
Guaifenesin	200–400 mg by mouth every 4 hours as needed	Expectorant. Loosens secretions to aid in their expulsion
Diphenhydramine	25 mg by mouth every 4 hours	Any first-generation antihistamine is suitable for use in cough. Anticholinergic properties are useful for reducing secretions and postnasal drip
Pseudoephedrine	30–60 mg by mouth every 4–6 hours as needed	Decongestants can be tried for UACS

CYP 2D6 cytochrome P450 isoenzyme 2D6, *UACS* upper airway cough syndrome

Persistent cough >3-week duration needs to be worked up for identification of cause, thus referral is required.

- Significant systemic illness
- Change in mental status
- Dyspnea (breathlessness)
- Pleuritic chest pain
- Prolonged or high fever
- Abnormal respiratory exam (e.g., wheezing, crackles, stridor)
- Increased work of breathing (e.g., respiratory rate >20 breaths/minute, using accessory muscles to breathe, unable to speak normally)
- Cyanosis (e.g., bluish or purple discoloration of lips/mouth, or fingers/hands, which may feel cold to the touch)
- Hemoptysis
- Suspicion of inhaled foreign body
- Dysphagia

The preceding symptoms all indicate a degree of severity that warrants urgent/emergency room attention. Significant systemic illness, prolonged/high fever, change in mental status, increased work of breathing, and cyanosis may be signs and symptoms of sepsis and/or impending respiratory failure. Pleuritic chest pain and hemoptysis require evaluation to rule out PE and assess for pneumonia, both of which require urgent/timely therapy.

- Urinary incontinence or vomiting associated with coughing
- Suspicion of lung cancer

For patients with the preceding signs and symptoms, timely evaluation is required by primary care provider or more urgently if the situation requires.

- Worsened HF symptoms: shortness of breath, orthopnea (e.g., requiring more pillows than normal to sleep), paroxysmal nocturnal dyspnea, peripheral edema, or weight gain.
- AECOPD (see three cardinal symptoms in AECOPD section)
- Asthma exacerbation not responding to initial therapy (see asthma exacerbation section above). If risk factors for fatal asthma exacerbation (see asthma section above), emergency attention is required.

The above represent worsened chronic conditions. Severity of symptoms, as well as patient risk factors, will dictate whether timely primary care or emergency referral is required. Many of these patients will require hospitalization.

Monitoring and Follow-Up

For patients with acute cough (<3-week duration), frequency of monitoring and follow-up will depend on initial assessment and triaging (i.e., referral to primary care vs. urgent care vs. self-care). For example, for many patients who are appropriate for self-management, and who have trialed a cough medication, it would be prudent to follow up with them in the next 1–7 days. Efficacy-monitoring parameters would include frequency of cough, quality and quantity of sleep, and amount of sputum production. Safety monitoring parameters would include common side effects of whatever medication was chosen. For example, safety monitoring for codeine would include questioning for drowsiness or constipation. For dextromethorphan, one would need to ask about serotonin toxicities if the patient is taking any other serotonergic drugs.

For patients with mild asthma exacerbation that is being managed at home, follow-up should occur within 12–24 hours to ensure the patient is improving and does not require further assessment and management.

For AECOPD or HF exacerbation, frequent follow-up would be needed for patients who have been sent with a home management plan from their primary care provider, to ensure that continued home management is appropriate and that they are improving. These patients would likely receive additional/intensified therapies, such as oral prednisone ± antibiotics for AECOPD and intensified diuretic therapy for HF. These patients are often complex and thus require diligent monitoring based on severity of illness and medica-

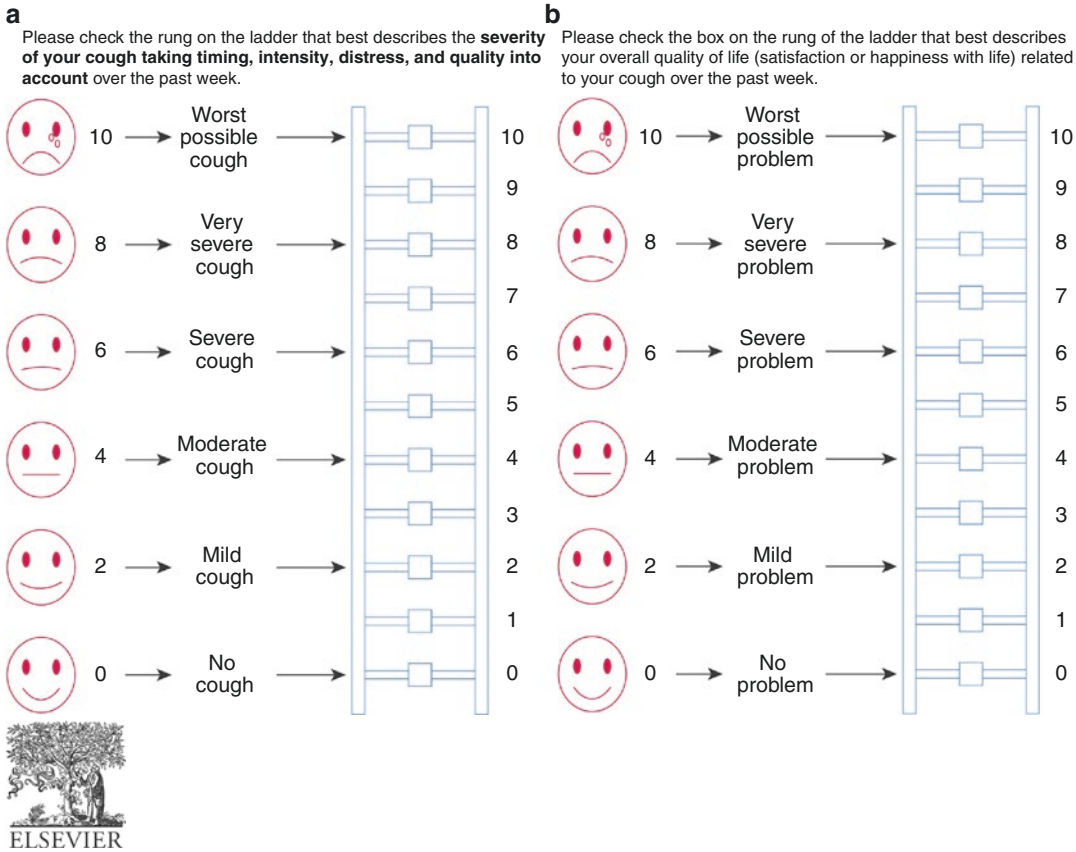


Fig. 5.2 Representative Punum ladders to assess (**a**) cough severity or (**b**) overall quality of life. (Reprinted from Irwin et al. [4], Copyright 2018, with permission from Elsevier)

tions prescribed. Monitoring parameters would include target symptoms (cough, dyspnea, daily weights, and edema for HF), as well as side effects from additional or intensified therapies.

ACCP recommends using a validated tool to assess patients at follow-up. Figure 5.2 shows validated tools for measuring severity of cough as well as cough-related quality of life. The scales may be used at baseline and at follow-up visits to measure treatment effects.

Clinical Pearls

Pharmacists play an important role in assessing and managing cough. A systematic approach to cough assessment is recommended and includes:

- Determine duration of cough.
- Look for red flags and refer if present.
- Use SCHOLAR or other structured questions to elicit key information such as symptoms, characteristics, past medical history, etc.
- If patient is appropriate for treatment at home, elicit their goals of therapy, and recommend symptomatic therapies if appropriate and desired.
- Monitoring and follow-up will be based on treatment plan, severity of symptoms, and underlying comorbidities.

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Nausea and Vomiting

6

Tara Leslie

Chapter Objectives

1. Describe the etiology, key symptoms, and treatment principles for patients presenting with nausea and/or vomiting due to common causes seen in pharmacy practice.
2. Apply a systematic approach to assess patients presenting with nausea and/or vomiting in order to determine the probable cause and provide appropriate guidance for next steps.
3. Identify the red flags in patients presenting with nausea or vomiting that should trigger referral to other health-care practitioners or urgent medical care.

Background

Nausea and vomiting are common conditions with variable etiology. In some cases, they are self-limiting but, in others, can be associated with an urgent and/or serious medical disorder. Pharmacists need to have awareness of the different potential causes of nausea and/or vomiting and the associated symptoms for each. Using a stepped approach to gathering important information, the pharmacist can begin to delineate the cause of the nausea and/or vomiting and quickly refer if a critical underlying issue is plausible. If serious concerns have been ruled out, or appear unlikely given the presentation and assessment, the pharmacist can take next steps to develop an appropriate treatment plan and/or provide reassurance.

Nausea can be defined as the inclination to vomit or a feeling in the throat or epigastric area that vomiting is imminent [1]. Vomiting is defined as the ejection or expulsion of gastric contents through the mouth with involuntary muscle contractions [1, 2]. Vomiting differs from regurgitation, where forceful contractions are absent [2]. The vomiting center (VC), within the lateral reticular formation of the medulla, organizes the vomiting response upon activation by afferent impulses. Afferent stimuli may originate directly from gastrointestinal tract (GIT) or other systems, extramedullary central nervous system (CNS) afferents, or the chemoreceptor trigger zone (CTZ). The CTZ can be easily triggered by nauseating substances as it is located within the area postrema and hence lies partially outside of the blood-brain barrier [3]. The pathogenesis of vomiting itself involves many different receptors including serotonergic, dopaminergic, histaminic, and muscarinic [3].

Several serious conditions requiring urgent medical care such as appendicitis, pancreatitis, stroke, and myocardial infarction can present with nausea and/or vomiting as part of their

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constellation of symptoms. Other less concerning causes include pregnancy, onset of an acute self-limiting gastric infection, exposure to nauseating medications, or experiencing different types of motion or electronic stimuli (motion sickness). Table 6.1 lists medication-related, disease-related, and other causes of nausea and/or vomiting.

It is important to note that nausea and/or vomiting can be distressing and unpleasant for patients even if the symptoms are due to self-limiting conditions. Further, if unresolved or prolonged, symptoms can lead to dehydration, hypovolemia, and consequential electrolyte, metabolic, and hemodynamic concerns. Ultimately, the goal is to treat the underlying cause of the nausea and/or vomiting as appropriate, eliminate the symptoms, and correct any sequelae such as dehydration.

Common Causes of Nausea and/or Vomiting in Pharmacy Practice

Gastroenteritis

Nausea and/or vomiting are symptoms commonly present in gastroenteritis, defined as inflammation of the stomach, small intestine, and/or large intestine [4, 5]. In addition to nausea and/or vomiting, most patients with gastroenteritis also present with diarrhea, and some may report fever, malaise, and/or cramping abdominal pain [4–6].

Table 6.1 Causes of nausea and/or vomiting

Medication causes	Disease causes	Other causes
Antimicrobials	Cardiac	Motion sickness
Cephalosporins	Acute myocardial infarction	Nausea and/or vomiting of pregnancy
Ketoconazole	CNS causes	Radiation therapy
Macrolides	Head trauma/brain injury	Recent excessive ingestion of alcohol
Metronidazole	Migraine	Recent surgery (postoperative nausea/vomiting)
Penicillins	Meningitis	
Antineoplastics	Stroke	
Cisplatin	Gastrointestinal	
Cyclophosphamide / Anthracycline Combinations	Appendicitis	
Dacarbazine	Cholecystitis	
NSAIDs	Gastroenteritis (viral, bacterial, parasitic)	
Diclofenac	Intestinal obstruction	
Ibuprofen	Pancreatitis	
Naproxen	Peptic ulcer disease	
Opiates	Genitourinary	
Codeine	Urinary tract infection (UTI)	
Fentanyl	Pelvic inflammatory disease (PID)	
Hydromorphone		
Morphine		
Oxycodone		
Others		
Amiodarone		
Bromocriptine		
Cyclosporine		
Fluoxetine (and other SSRIs)		
Iron supplements		
Ketamine		
Metformin		
Mycophenolate		
Nitrous oxide		
Potassium supplements		
Ropivacaine (and other anesthetics)		

NSAIDs nonsteroidal anti-inflammatory drugs

Most cases of acute gastroenteritis are self-limiting and caused by an acute infectious process. The infective source is most commonly of viral origin (70%) and can include norovirus, rotavirus, and adenovirus [4, 5]. However, bacterial pathogens such as *Shigella*, S*almonella*, *E coli*, or *Campylobacter* or parasites such as *Giardia*, *Amebiasis*, or *Cryptosporidium* can also be implicated [4]. Patients with acute gastroenteritis may report exposure to a sick friend/family member, travel, or ingestion of potentially spoiled food (e.g., attendance at a potluck) within their recent history. Although the exact mechanism is unknown, vomiting due to gastroenteritis is believed to be related to stimulation of the vagus nerve or serotonin receptors in the GIT, which send impulses to the VC [5].

The primary supportive treatment of acute gastroenteritis is largely preventing dehydration or providing appropriate rehydration [4]. Patients with severe dehydration require urgent referral for additional assessment and IV rehydration. For oral rehydration, options include commercial electrolyte replacement solutions, diluted fruit drinks, or diluted commercial sport drinks [4]. Given the numerous receptors involved in the pathogenesis of vomiting, appropriate use of agents such as dimenhydrinate, ondansetron, or metoclopramide can be useful to halt nausea and/or vomiting symptoms.

Motion Sickness

Nausea, with or without vomiting, is the signature symptom of motion sickness, a syndrome coinciding with the experience of certain types of motion [7] or visual experiences [8]. Examples of activities related to motion sickness are travel by aircraft, boat, or motorized vehicle, going on an amusement park ride, or the use of technology with 3D displays. The pathogenesis of motion sickness is thought to be related to a mismatch between the sensory and actual patterns of vestibular and visual systems [7, 8]. Motion sickness often starts with minor symptoms such as a feeling of gastric fullness, malaise, or drowsiness, and then progressing to nausea [7]. Patients may also experience belching, headache, sweating, dizziness, hypersalivation, and facial pallor [7, 8].

If the motion sickness stimuli cannot be avoided, preventative strategies should be employed. Non-pharmacologic suggestions include habituation by slowly introducing the motion, maintaining a view of the true visual horizon, or choosing a location in the vehicle that minimizes the motion such as over the wing of an airplane [7]. If medication is required, efficacy is improved if combined with behavioral strategies and if administered prior to motion exposure or quickly after the onset of symptoms. Transdermal scopolamine is often the preferred choice for motion sickness in suitable patients given it is less sedating than other options such as dimenhydrinate.

Medication-Induced Nausea and Vomiting

Exposure to medications can be a common cause of nausea and/or vomiting and occurs through a variety of mechanisms. Some medications, such as antibiotics, can be locally irritating to the GIT leading to abdominal discomfort followed by nausea and/or vomiting. Symptom onset typically occurs shortly after ingestion and patients may feel relief after emesis. Preventative measures include administration of the offending medication with food and a full glass of water. If ineffective, avoiding the medication in sensitive individuals could be considered if an appropriate alternative agent exists.

Nausea and/or vomiting are common side effects experienced by patients initiated on opioids. This effect appears to be dose-related, and tolerance usually (but not always) occurs within days to weeks after introduction [9]. The exact etiology of opiate-induced nausea and/or vomiting (OINV) is uncertain. Postulated mechanisms include a combination of heightened vestibular sensitivity, direct exposure with the chemoreceptor trigger zone, and slowed gastric emptying [9]. Exposure to volatile anesthetics and nitrous oxide are involved with postoperative nausea

and/or vomiting (PONV) and can be worsened by the use of opioids [10].

Perhaps the most notorious group of medications known to cause nausea and/or vomiting are cytotoxic antineoplastic agents. The etiology of antineoplastic-induced nausea and/or vomiting (AINV) is complex and not fully delineated. Signals from the chemoreceptor trigger zone, cerebral cortex, GIT, and other areas are sent to the VC causing subsequent signals to effector organs leading to nausea and/or vomiting. Numerous neurotransmitter receptors are involved such as serotonin (5-HT3), dopamine, and neurokinin 1 (NK1) [11]. The emetic potential of the antineoplastic agent(s) to be administered is the most important factor to consider when determining the requirement and regimen for AINV prophylaxis. A classification system of emetogenicity of anticancer drugs was developed by Hesketh et al. in 1997 [12] and further refined most recently by Jordan et al. in 2017 [13]. Each agent is categorized as high, moderate, low, or minimal emetic risk based on the agent's potential to cause vomiting in patients who don't receive prophylaxis [12, 13].

AINV can be classified as acute, delayed, anticipatory, breakthrough, or refractory. Acute AINV occurs within the first 24 hours after administration of the medication with the intensity peaking at 5–6 hours. Delayed AINV occurs more than 24 hours after drug administration and can last for 6–7 days [11]. Delayed nausea is more common than acute and can often be more severe and treatment resistant. Anticipatory AINV is considered a conditioned response and develops prior to a patient's next chemotherapy treatment [11]. Breakthrough AINV is a term for nausea or vomiting that occurs despite appropriate prophylaxis. Patients receiving high or moderately emetogenic antineoplastic therapy require combination therapy in order to prevent acute and delayed AINV as well as an agent to treat breakthrough nausea [14]. Hesketh et al. have published updated guidelines in 2017 on the prescribing of antinauseant/antiemetic combination regimens for AINV and radiation-induced nausea and/or vomiting (RINV) [14]. Combinations for prevention of AINV with highly emetogenic chemotherapy may include a serotonin (5-HT3) antagonist such as ondansetron, a neurokinin 1 (NK1) receptor antagonist such as aprepitant, dexamethasone, and olanzapine [14].

Nausea and Vomiting of Pregnancy

Nausea and/or vomiting are common symptoms of pregnancy, affecting 50–80% of pregnant women [15]. In some cases, nausea and vomiting of pregnancy (NVP) is mild and temporary, but for some women it can be more severe, debilitating, and long lasting [15]. Although commonly referred to as morning sickness, pregnant women may experience episodes of nausea and/or vomiting throughout the day. Symptoms typically start weeks after conception, peak around 10–16 weeks gestation, and subside around 20 weeks gestation [6]. Hyperemesis gravidarum (HG) is a severe and persistent type of NVP that can lead to dehydration, weight loss, and electrolyte imbalance that can potentially harm both the mother and unborn child [15]. The pathogenesis of NVP has been postulated to be related to a rise in human chorionic gonadotropin. However the evidence to support this theory is controversial and hence the exact etiology remains unknown [16].

Women of childbearing age who present with nausea and/or vomiting should be asked about possible pregnancy including the date of last menses. If pregnancy is suspected, but not yet confirmed, a pregnancy test should be recommended. The outcome will help inform the differential diagnosis and assist in selecting safe treatment options as appropriate. To avoid misdiagnosis, other potential causes should be assessed and ruled out prior to concluding symptoms are due to pregnancy alone. If symptoms are negatively impacting the pregnant woman's quality of life or if hydration or nutritional status is of concern, the patient should be referred. In addition, referral for prenatal care should be provided for all women suspecting or recently discovering a pregnancy.

Dietary and lifestyle changes are often the first treatment strategy for NVP. Adequate rest, avoiding strong odors, separating solid food intake from liquid intake, eating smaller bland meals

more frequently, and avoiding fatty foods are reasonable recommendations although limited evidence exists to support them [15]. Given the devastating historical impact of thalidomide, hesitancy exists with the use of pharmacotherapy for NVP in both patients and health care providers. However, if a non-pharmacologic approach is ineffective, pharmacotherapy may be warranted. The Society of Obstetricians and Gynecologists of Canada (SOGC) published Clinical Practice Guidelines for NVP in 2016 authored by Campbell et al. [15]. Within these guidelines, a treatment algorithm is provided to assist in NVP pharmacotherapy decisions [15].

Symptom Assessment (SCHOLAR)

Nausea and/or vomiting is a common presentation that can be associated with a vast array of underlying causes. The etiology can vary from a mild self-limiting illness to a serious condition requiring urgent referral. A careful and thorough symptom assessment using a systematic process is essential. Information such as the characteristics of the nausea and/or vomiting, the symptom onset and behaviors, other associated symptoms, and patient history provide key clues to the underlying etiology and appropriate next steps. These features and the associated etiology and next steps are summarized in Table 6.2.

Symptoms

- In addition to the nausea and/or vomiting, did you experience any other symptoms?
  - Do you have changes in your stools such as diarrhea or constipation?
  - Do you have a fever?
  - Do you have any pain? If yes, can you describe the location, type, and intensity of the pain?
  - Do you have any neurologic symptoms such as headache, dizziness, or confusion?

Clarifying the symptoms associated with the nausea and/or vomiting will help to determine the cause and identify red flags. Intense pain can be impetus for urgent referral. Abdominal pain can be associated with appendicitis, acute cholecystitis, or pancreatitis. Lower abdominal, flank, or pelvic pain can be associated with a genitourinary type infection, while chest pain can be associated with an acute myocardial infarction. Diarrhea and fever often accompany nausea and/or vomiting in gastroenteritis. Constipation can be indicative of a bowel obstruction, whereas melena stools (black tarry appearing feces) can suggest bleeding in the GIT. Nausea and/or vomiting can accompany migraine headache. However, worrisome neurologic symptoms such as confusion with or without headache warrant urgent referral.

Characteristics

- Are you experiencing nausea, vomiting, or both?
  - Do the symptoms occur in a certain pattern? For example, at the same time each day?
- Can you describe the nausea?
  - Is it constant or periodic?
  - If periodic, how frequent?
  - On a scale of 1–10, how severe is the nausea?
- Can you describe the vomiting?
  - How frequently (or how many times) have you vomited?
  - What does your vomitus look like? (food present, blood present, coffee-ground appearance, or other)
  - Does it happen without warning and/or projectile?

The characteristics of the nausea and/or vomiting such as appearance, severity, frequency, and timing provide helpful details to assist in identifying a cause. Nausea can be present without vomiting in medication-related causes or motion sickness. Projectile vomiting without previous nausea can be a symptom of an intracranial disorder.

Vomitus with bright red blood (known as hematemesis) or a coffee-ground appearance is

Table 6.2 Description of key factors for differential diagnosis of nausea and vomiting (NV)

Description of additional symptoms and/or characteristics	Possible cause	Management strategies
Often presents with symptoms of diarrhea and may also present with headache, cramping abdominal pain, fever, malaise Onset is often following recent contact with a sick friend/family member, recent travel, or recent ingestion of potentially spoiled food/drink	Gastroenteritis	Assess severity and duration Consider pharmacotherapy with antinauseant/antiemetic or referral if IV hydration or culture required
Motion-related (aboard plane, ship, car) or electronic stimuli-related Symptoms can include vertigo belching, sweating, dizziness, hypersalivation, and facial pallor	Motion sickness	Preventative strategies; avoiding motion/stimuli (if reasonable), habituation, or pharmacotherapy
Recent ingestion of medications, administration of chemotherapy, radiation therapy, or surgery requiring general anesthetic	Medication-induced NV or antineoplastic-induced NV or radiation-induced NV or postoperative NV	Assess severity and duration Determine offending agent and explore strategies to mitigate symptoms or avoid the agent If these strategies are not reasonable/appropriate, consider pharmacotherapy to prevent and/or treat symptoms
Timing of nausea/vomiting may be in the morning Amenorrhea or positive pregnancy test Onset is prior to 12 weeks gestation Lack of other causes of NV	NV of pregnancy	Consider lifestyle/dietary measures or pregnancy safe pharmacotherapy if ineffective Referral for pre-natal care and/or refractory symptoms
Severe abdominal pain Onset may be abrupt	Appendicitis, acute cholecystitis, pancreatitis, intestinal obstruction	Prompt referral
Polydipsia and/or polyuria Possible altered mental status and/or fruity breath odor History of diabetes	Diabetic ketoacidosis (DKA)	Prompt referral
Dyspepsia, heartburn, or epigastric pain Symptoms of hematemesis, coffee-ground vomitus, bloody stools, melena (dark tarry) stools	Gastrointestinal bleed, peptic ulcer disease, cancer	Consider pharmacotherapy for mild symptoms of dyspepsia and referral in the case of more serious symptoms Urgent referral required for hematemesis
Symptoms include headache, neurologic symptoms, and/or disorientation Emesis can be projectile Possibly following trauma to the head	Intracranial disorders, stroke	Urgent referral for additional investigations/workup
Headache possibly with aura and/or photophobia May have nausea without emesis or headache may diminish after emesis Patient history of migraine	Migraine	Treat underlying cause of migraine Referral if concerns of intracranial disorder
Chest pain, may be described as crushing, may radiate to jaw or left arm	Myocardial infarction	Urgent referral for additional investigations/workup
Symptoms may include headache, stiff neck, fever	Meningitis	Urgent referral for additional investigations/workup
Symptoms may include fever, dysuria, vaginal discharge, and/or suprapubic or flank pain	UTI or PID	Referral for additional workup and antimicrobial treatment

PID pelvic inflammatory disease, *UTI* urinary tract infection

associated with a bleeding gastric or duodenal ulcer. When a large amount of blood is being lost, hematemesis may be present and should be considered a medical emergency. The coffee-ground appearance results from a smaller volume of blood sitting in the GIT and becoming partially digested. In both cases referral is prudent.

Frequency of vomiting can provide important insight into the patient's current hydration status and possible sequelae of dehydration. In addition, it informs the clinician of the patient's ability to tolerate oral medications if pharmacotherapy is indicated after completion of the assessment. In NVP, symptoms are sometimes (but not always) more intense in the morning. Severity helps establish a numerical baseline for symptom comparison after intervention.

History

- Has the nausea and/or vomiting happened before?
- Have you eaten/drunk anything out of the ordinary (potlucks, restaurants, questionable water, excessive alcohol, etc.)?
- Have you taken any new medications or recreational drugs?
- Have you traveled recently? Where and when?
- Have you had any recent contact with someone having similar symptoms?
- Have you recently injured yourself or hit your head?
- If female patient of childbearing age: Is there any chance you are pregnant? And (if appropriate) when was your last menses?

A positive travel history, contact with a similarly sick individual, or exposure to potentially contaminated food/water can suggest infectious gastroenteritis. Assessment of other features such as accompanying symptoms, time since onset, symptom severity, and location of travel (if applicable) is important in determining if a patient with suspected gastroenteritis requires referral for cultures, antibiotics, or IV rehydration.

Recent ingestion of nauseating medications implies a medication cause. Nausea and/or vomiting are common after acute alcohol intoxication and can also be related to recreational drug use. Patients suspected to be at risk of alcohol poisoning or drug overdose require immediate medical attention. Patients with nausea and/or vomiting related to trauma, specifically a head injury, should also be referred to an acute care medical facility. Potentially pregnant patients may be experiencing NVP but other causes should also be explored.

Onset

- When did the nausea and/or vomiting begin?
  - For patients receiving antineoplastic medications, when did the nausea/vomiting begin in relation to your chemotherapy treatment (within 24 hours, after 24 hours, before the treatment began)?
- Did the nausea and/or vomiting start suddenly or gradually?
- Are there certain times of the day when the nausea is worse or vomiting is more frequent?

Vomiting that has persisted for an extended period of time can lead to concerns of dehydration and electrolyte disturbances. Sudden onset can trigger suspicion that the cause is recent exposure to an infectious source or nauseating substance. Although not always, NVP symptoms may be more frequently experienced in the morning. Onset is important for determining the type of AINV (acute, delayed, breakthrough, or anticipatory) for patients receiving chemotherapy treatment.

Location

- Not applicable

Aggravating Factors

- What makes the nausea and/or vomiting start or worsen?

  - Are the symptoms triggered or worsened by certain odors?
  - Are the symptoms associated with specific types of motion or activities (electronic games/simulations)?
  - Do the symptoms occur after ingestion or administration of certain foods or medications?
  - In the case of AINV, are there specific triggers that worsen your nausea and/or vomiting (such as the anticipation of the next chemotherapy administration)?

Responses to these questions can further assist the clinician to identify the cause of the symptoms (e.g., motion sickness, NVP, or medication-induced nausea and/or vomiting). It can also provide insight into preventative measures that can be employed in the future.

Remitting Factors

- Have you tried anything for nausea and/or vomiting in the past? (Explore pharmacologic and non-pharmacologic interventions.)
  - Did any of these interventions diminish or eliminate the nausea and/or vomiting?
  - Did any interventions make the nausea and/or vomiting worse?
  - Did you experience any side effects from the intervention(s) that helped?
  - (If a medication(s) has helped in the past) How often do you take the antinausea medication?

Various treatment options exist for nausea and/or vomiting with varying efficacy depending on the underlying cause of the nausea and/or vomiting (Table 6.3). Hence, treatment recommendations including the choice of antinauseant(s) must first be guided by the cause (e.g., motion sickness, NVP, or AINV). Changes in the treatment plan, such as the pharmacotherapy agent or dose, are influenced by the successes and failures of past or current interventions. For example, an assessment of antinauseants used previously is extremely important for patients with AINV to determine how to treat breakthrough symptoms and escalate prophylactic treatment for future chemotherapy cycles. In many cases, women with NVP should have failed non-pharmacologic options prior to starting a pregnancy-safe pharmacotherapy agent.

Patient-Specific Characteristics

Patient factors are important considerations for assessing the need for referral or proper selection of antinauseants.

Pregnancy

As mentioned earlier, women of child bearing age should be questioned regarding possible pregnancy and if uncertain, a pregnancy test should be done. For pregnant women less than 20 weeks gestation, NVP is a reasonable diagnosis when all other causes of nausea and/or vomiting have been ruled out. If an antinauseant is required, selection should be done based on both the cause of the nausea and consideration to safety for both mother and unborn child.

Age

Very young or elderly patients may be at higher risk of dehydration and resulting complications.

Past Medical History

Identifying the patient's comorbidities can assist in determining potential underlying causes of nausea and/or vomiting and aid in appropriate antinauseant selection. For example, consider a patient with diabetes. Nausea and/or vomiting could be associated with a serious cause such as diabetic ketoacidosis. In addition, diabetic

Table 6.3 Summary of select antinauseants/antiemetics [10, 14, 15, 17, 18]

Antiemetic agent(s)		Clinical use in adults	Select warnings
Dexamethasone		Prevention of AINV in combination with other antiemetics	Side effects include hyperglycemia, hypertension, fluid retention, insomnia, mood changes
Dimenhydrinate		Management of nausea/vomiting related to GE, RINV, PONV, DINV Management of vertigo or nausea/vomiting related to motion sickness Management of NVP[a]	Contraindications include narrow-angle glaucoma, chronic lung disease, difficulty in urination due to prostatic hypertrophy Due to CNS depressant effects, avoid with alcohol May cause drowsiness
Doxylamine succinate with pyridoxine		Management of NVP[a]	Contraindications include uncontrolled asthma, narrow-angle glaucoma, stenosing peptic ulcer, and coadministration with monoamine oxidase inhibitors (maois) Common side effects include somnolence
Metoclopramide		Prevention of PONV or AINV Treatment of AINV[a], RINV[a] Management of NVP[a]	Can elevate prolactin levels and/or cause extrapyramidal symptoms Side effects include diarrhea and drowsiness
Neurokinin 1 (NK1) Receptor antagonist Aprepitant Fosaprepitant		Prevention of AINV in combination with other agents Prevention of PONV (aprepitant only)[a]	Several drug interactions: aprepitant is a substrate, moderate inhibitor, and inducer of CYP 3A4 and an inducer of CYP 2C9
Phenothiazines Prochlorperazine Chlorpromazine Promethazine		Management of nausea and/or vomiting Treatment of AINV (prochlorperazine)[a] Management of motion sickness (promethazine)[a]	Can cause extrapyramidal reactions, tardive dyskinesia, QTc prolongation Use with extreme caution in the elderly Contraindicated in severe depression and Parkinson's disease
Serotonin (5HT3) Antagonists	Ondansetron	Prevention of AINV and RINV Prevention and treatment of PONV Undifferentiated N/V managed in the ER setting[a] Management of NVP[a]	Increased risk of serotonin syndrome Dose-dependent QTc interval prolongation Common side effects include headache and constipation
	Granisetron	Prevention of AINV and RINV	
	Palonosetron	Prevention of AINV	
Scopolamine base (transdermal patch)[b]		Prevention of symptoms of motion sickness	Contraindications include angle-closure glaucoma; prostatic hyperplasia; paralytic ileus; myasthenia gravis May cause drowsiness, orthostatic hypotension, and dry mouth Elderly patients are at increased risk of CNS adverse effects Patients should wash hands well immediately after applying patch

AINV antineoplastic-induced nausea and vomiting, *DINV* drug-induced nausea and/or vomiting, *ER* emergency room, *GE* gastroenteritis, *NVP* nausea and vomiting of pregnancy, *PONV* postoperative nausea and vomiting, *RINV* radiation-induced nausea and vomiting

[a]Not an approved Health Canada indication (off-label use)

[b]Health Canada considers it to be a natural health product

patients are much more likely to have quick complications from dehydration or reduced oral intake. Another example is a patient with a notable history of cardiac arrhythmia. Serotonin (5-HT3) antagonists, such as ondansetron, have a known risk of QT prolongation and may be an inappropriate choice.

Medication History

Obtaining a best possible medication history is important to assess medication causes of nausea and/or vomiting and also to avoid potential drug interactions with antiemetic agents. For example, identifying the specific antineoplastic drugs a cancer patient is receiving is important in order to assess its emetogenic potential and appropriate prophylaxis. In less extreme cases, a medication history may elucidate the offending agent and an alternative administration strategy or therapeutic agent may be easily initiated. For drug interaction considerations, an example is a patient with motion sickness who is already taking anticholinergic medications. This patient may be unable to tolerate the additional anticholinergic effects of scopolamine.

Red Flags

It is essential that assessment of the patient with nausea and/or vomiting include considerations for underlying causes that can be serious and, in some cases, life-threatening. Presence of any of the following red flags indicates that prompt referral to an urgent care center is warranted.

- *Severe pain:* Severe pain in the chest, abdomen, or pelvis can indicate a serious underlying cause such as myocardial infarction, appendicitis, pancreatitis, cholecystitis, peptic ulcer disease, intestinal obstruction, or pelvic inflammatory disease.
- *Head trauma or neurologic symptoms or disorientation:* A history of head trauma or the presence of neurologic deficits requires urgent referral to assess for stroke or a brain injury. Disorientation with neurologic symptoms, fever, and stiff neck is associated with meningitis.
- *Symptoms suggesting infection requiring antibiotics:* Presence of additional symptoms such as fever with dysuria and/or urinary frequency suggests a urinary tract infection. Presence of fever with vaginal discharge and suprapubic pain suggests pelvic inflammatory disease. If gastroenteritis due to a serious bacterial or parasitic cause is suspected, patients should be referred for additional workup.
- *Vomitus containing blood, resembling ground coffee, and/or melena stools:* Nausea and/or vomiting with melena stools and/or vomitus that contains blood or has the appearance of coffee grounds are suggestive of gastrointestinal bleeding.
- *Severe, refractory, and/or prolonged nausea and/or vomiting:* Persistent vomiting can lead to dehydration, electrolyte disturbances, and metabolic issues. Referral for possible parenteral hydration and treatment is required.
- *Dehydration:* Patients with signs of substantial dehydration such as dry mucus membranes, reduced urine output, and/or mental status changes should be referred.

Additional Assessment Considerations

Additional workup, including physical exam, may be indicated depending on the working differential diagnosis. When the suspected cause of nausea and/or vomiting is parasitic or bacterial gastroenteritis, stool and/or blood cultures may be appropriate. In the event of significant dehydration, laboratory tests are warranted to explore potential electrolyte or metabolic disturbances. If a serious underlying cause is suspected, additional tests are often required to explore and/or confirm the diagnosis. These may include diagnostic imaging, endoscopic procedures, laboratory tests, cultures, or an electrocardiogram.

Follow-up assessment is recommended for patients with nausea and/or vomiting. Patients with AINV and an ongoing chemotherapy treatment schedule should be encouraged to keep a diary of nausea and vomiting episodes. Patients

with other medication-induced nausea and/or vomiting should be monitored for the effectiveness of the intervention (change in administration instructions or change in therapeutic option) at minimizing or eliminating nausea/vomiting symptoms while still ensuring the original treatment goals are achieved. Patients with suspected viral gastroenteritis should be monitored for resolution of symptoms and adequate rehydration. As part of managing NVP, patients should be monitored for symptom improvement and maintenance of adequate nutrition, hydration, and prenatal care.

Clinical Pearls

- Pharmacists are very accessible to the public and often a patient's first point of contact when seeking health care for nausea and/or vomiting.
  - Pharmacists need to be knowledgeable in the assessment, treatment, and monitoring for common and self-limiting causes of nausea and/or vomiting.
  - Identification of red flags is important to ensure patients are referred to urgent or prompt medical attention when required.
- Assessment of nausea and/or vomiting involves the following key steps:
  - Symptoms, characteristics, history, and onset to ascertain the probable cause of nausea and/or vomiting and recognize possible red flags
  - Aggravating and/or remitting factors to further clarify the possible cause and inform the decision of next steps
  - Development of an individualized treatment and monitoring plan informed by the cause of the nausea and/or vomiting along with important patient-specific factors

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Diarrhea

7

Elizabeth Glashan and Sherif Hanafy Mahmoud

Chapter Objectives

1. Outline common etiologies of acute diarrhea.
2. Assess patients with diarrhea.
3. Identify patients who are candidates for pharmacological therapy (antibiotics, antidiarrheal), and nonpharmacological therapy (oral rehydration solution or other means of fluid repletion).
4. Identify red flag symptoms that prompt referral and urgent assessment.

Background

Diarrhea is a common ailment that patients often seek treatment for. US data suggest an incidence of 0.6 bouts of diarrhea per person per year [1]. Canadian sales for over-the-counter (OTC) remedies for diarrhea exceeded $50 million CAD in 2008 [2]. Pharmacists play an important role in the assessment and management of patients with diarrhea. They can identify patients who need urgent medical attention, those who are appropriate for self-care, and anyone in between. Diarrhea assessment involves gathering a focused history from the patient, concentrating on clinical features, exposure history, presence or absence of red flags, and key patient-specific factors. Once the pharmacist has gathered the necessary information, they can move on to next steps such as prescribing an OTC medication, or referral to the family physician or the emergency department.

Diarrhea is a syndrome characterized by a clinically significant increase in bowel movement frequency or volume. It is often defined as ≥3 loose bowel movements in a 24 h period, or >250 g stool/day. Acute diarrhea is defined by symptoms lasting up to 14 days, whereas persistent diarrhea lasts 14–30 days, and chronic diarrhea has >30 days duration [1]. Diarrhea can also be classified according to the underlying mechanism into osmotic, secretory, and inflammatory. Osmotic diarrhea results when nonabsorbable, osmotically active substances are present and draw excess water into the intestinal lumen (e.g., magnesium hydroxide). Secretory diarrhea occurs when intestinal secretions into the lumen exceed absorption. This can be in response to toxins from enteric pathogens, or due to malabsorption of luminal molecules such as bile salts in the setting of decreased absorptive area post bowel resection. Inflammatory diarrhea occurs when the intestinal epithelium is damaged by inflammation, resulting in exudation of blood and

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pus into the lumen. Infection and inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis are common causes of inflammatory diarrhea [3].

Etiology

Acute diarrhea can be grouped into the following categories: infectious, drug-related, and disease-related.

Infectious Diarrhea

Infection is the most common cause of acute diarrhea. In the United States, the incidence of acute infectious diarrhea has been reported by the Centers for Disease Control and Prevention (CDC) to exceed 40 million cases annually, costing over $150 million in healthcare expenditure [4]. The infectious agents can be viral, bacterial, or protozoan. Table 7.1 depicts examples of the most common pathogens. All infectious agents of acute diarrhea can be acquired from either improperly handled food (e.g., poultry, shellfish, imported fruits and vegetables) or fecally contaminated water sources. In most cases, stool culture and microscopy fail to identify the causative agent and are not routinely recommended. In cases associated with bloody diarrhea, or other severe symptoms (e.g., ≥6 stools per day, fever, signs of dehydration, severe abdominal pain), or duration of symptoms >7 days, referral is warranted. These patients will likely benefit from microbiological testing and/or antimicrobial therapy [4].

Clostridium Difficile Infection

Clostridium difficile is an important pathogen that causes significant morbidity and mortality. An estimated 37,900 cases of *C. difficile* infection (CDI) occurred in Canada in 2012, costing over $280 million CAD [7]. Diarrhea is the most common symptom, with colitis, toxic megacolon, need for surgery, and death as possible complications. *C. difficile* is an anaerobic, gram positive, sporulating, toxin-producing organism that is commonly present in the human gastrointestinal (GI) tract. Many people are asymptomatic carriers, due to the protective effects of our normal flora. Antibiotic therapy is a major risk factor for CDI, due to disruption of our microbiome. Virtually any antibiotic can predispose one to CDI. The following are antibiotics that have been strongly associated with CDI [8, 9]:

- Fluoroquinolones (moxifloxacin > ciprofloxacin > levofloxacin)
- Cephalosporins
- Clindamycin
- Carbapenems

Table 7.1 Common infectious diarrhea pathogens and exposure sources [1, 4–6]

Organism group	Organism	Possible exposure source
Viruses	Norovirus	Outbreaks common in restaurants, healthcare facilities, schools, daycares, etc.
	Rotavirus	
	Enteric adenovirus	
Bacteria	*Eschericia coli* (enterotoxigenic)	Travel to resource-limited areas
	Shigella spp.	
	Campylobacter spp.	
	Salmonella (non-typhoidal)	
	Clostridium difficile	Antibiotic exposure, hospitalization, gastric acid suppression, and immunosuppression
Protozoa	*Giardia lamblia*	Daycare, drinking untreated stream water (known as "beaver fever")
	Cryptosporidium spp.	Public swimming pools, daycare
	Entamoeba histolytica	Travel to resource-limited areas, MSM

MSM men who have sex with men, *spp*. species

Antibiotics with relatively lower risk for causing CDI [9]:

- Aminoglycosides
- Trimethoprim-sulfamethoxazole
- Tetracyclines
- Metronidazole

In addition to antimicrobials, observational data suggest an association between proton pump inhibitors (PPIs) and CDI, highlighting the importance for PPI deprescribing when appropriate [8]. Decreased killing of spores due to reduced gastric acid is thought to be the mechanism underlying this association.

Ingestion of *C. difficile* spores is the primary mode of transmission. The spores are easily spread because they remain viable on inanimate objects for long periods of time. *C. difficile* spores are not reliably removed by hand sanitizer, so hand washing with soap and water is preferred in the setting of confirmed or suspected CDI. *C. difficile* has become an important pathogen in the community as well as the hospital [8]. Pharmacists play a critical role in identifying patients who are at risk for CDI. For any patient with recent antibiotic exposure, and new onset diarrhea, CDI must be considered and differentiated from non-CDI antibiotic-associated diarrhea (AAD). This can be difficult, as up to 35% of patients who take antibiotics will get diarrhea, most of whom do not have CDI [10, 11]. In general, AAD is milder and of shorter duration. Patients with CDI must not receive loperamide, diphenoxylate, or other antimotility agents, as they can precipitate toxic megacolon. Since the infection can progress to severe illness, curative antibiotics should be started promptly once CDI is suspected and they should not be withheld for stool-testing results [8]. Reassessment of the culprit antimicrobials is also important, and they should be discontinued if their risk outweigh their benefits. There is insufficient evidence at this time to support routine use of probiotics for the treatment or prevention of CDI [8], but some patients may wish to use them for this purpose.

Action items for suspected CDI:

- Refer to family physician or emergency room for stool sample, further assessment, and prompt initiation of antibiotic treatment when appropriate (metronidazole or oral vancomycin).
- Assess current antibiotics for appropriateness (i.e., assess for opportunity to hold causative antibiotics).
- Hold PPIs if they are not needed.
- Avoid Loperamide and other antimotility agents.

After an initial episode of CDI, up to 25% of individuals will experience a recurrence. Risk factors for recurrence include age > 65 years, need for ongoing antibiotics during therapy for CDI, and immunosuppression [12]. Recurrent CDI is associated with 33% increased risk of mortality at 180 days compared to those who do not suffer a recurrence [8].

Traveler's Diarrhea

Up to 40–60% of travelers going from resource-rich to resource-limited countries will develop diarrhea [13]. The symptoms are usually mild and self-limited. Most cases should not be treated with antibiotics. Antimicrobial therapy should be reserved for those with more severe symptoms such as fever, blood and pus in the stool, or diarrhea that substantially interferes with travel activities. Symptomatic therapies such as loperamide or bismuth can be used to treat mild-to-moderate symptoms. Antimotility agents should not be used for those with severe symptoms, unless antibiotics are also prescribed [13]. Of note, bismuth subsalicylate has been studied as a prophylactic agent against traveler's diarrhea (TD), with a success rate of 61% when taken at the recommended dose of 2 tablets 4 times a day, which equals 2.1 g per day [4]. An oral vaccine for prevention of TD is available, however, overall efficacy and costliness limit its use.

Medication-Related Diarrhea

Any newly started medication should be considered as a possible culprit for new onset diarrhea.

Many medications can cause this side effect, especially at the beginning of therapy. Table 7.2 lists drugs that are known to be common or important causes of diarrhea. In addition to the drugs in Table 7.2, opioid withdrawal is a medication-related cause of diarrhea that is frequently overlooked.

Disease-Related Diarrhea

All patients with persistent and chronic diarrhea should be referred to a physician for further assessment. This is because chronic illnesses are more likely to be the cause. Inflammatory bowel diseases like Crohn's disease and ulcerative colitis have severe sequelae if left untreated. Chronic secretory diarrhea can be caused by pancreatic insufficiency (malabsorption), as well as neuroendocrine tumours (e.g., carcinoid syndrome). Fecal impaction seen in severe constipation can lead to overflow diarrhea, as unformed stool bypasses the impaction. Celiac disease, food intolerance, diverticulitis, and certain malignancies are all further examples of chronic conditions associated with diarrhea [3]. Detailed discussion of these disease states is beyond the scope of this chapter.

Table 7.2 Drugs implicated to cause diarrhea [3, 14, 15]

Type of diarrhea	Implicated drugs
Osmotic diarrhea	Acarbose Antibiotics ACE inhibitors Enteral feeds Oral magnesium supplements or laxatives Sugar alcohols (mannitol, sorbitol, xylitol) Osmotic laxatives (e.g., lactulose, PEG 3350)
Secretory diarrhea	5-ASA derivatives Antibiotics Anticholinergics (constipation > diarrhea) [16] Antineoplastics Gold salts Metformin Digoxin Calcitonin Carbamazepine Cholinesterase inhibitors Colchicine Cimetidine Caffeine Prostaglandins (e.g., misoprostol) Simvastatin NSAIDs Stimulant laxatives Theophylline
Diarrhea due to altered motility	Cholinesterase inhibitors Cholinergic drugs (e.g., bethanechol) Irinotecan Macrolide antibiotics Metoclopramide Thyroid hormones
Inflammatory diarrhea	Antibiotics Albendazole Cimetidine Carbamazepine Chemotherapy agents Cocaine Etidronate Flutamide Gold salts Statins Immunosuppressants Itraconazole Methyldopa NSAIDs Isotretinoin Olmesartan (sprue-like enteropathy) PPIs Ranitidine SSRIs Stimulant laxatives Tyrosine kinase inhibitors TMP/SMX
Fatty diarrhea	Aminoglycosides Gold salts Cholestyramine Colchicine HAART Laxatives Methyldopa Octreotide Orlistat Tetracyclines

ACE angiotensin-converting enzyme, *HAART* highly active antiretroviral therapy, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PEG* polyethylene glycol, *PPIs* proton pump inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *TMP/SMX* trimethoprim-sulfamethoxazole, 5-*ASA* 5-aminosalycilyc acid

Symptom Assessment (SCHOLAR)

Patient assessment using the SCHOLAR approach provides a systematic framework to elicit necessary information, clarify the differential diagnosis, and identify red flag features. Figure 7.1 depicts the initial assessment and general management approach to diarrhea. The following questions are suggested in order to assess patients presenting with diarrhea:

Symptoms (Main and Associated Symptoms)

- Please describe your symptoms.
- Do you have a fever?
- Have you been vomiting as well?
- Do you have any viral symptoms like sore throat, cough, or myalgias?
- Do you have severe abdominal cramping?
- Do you have signs or symptoms of dehydration (dry mouth, dark urine, decreased urine output, thirst, dizziness, weight loss)?

Exploring the patient's main and associated symptoms will help clarify the differential diagnosis as well as identify red flag symptoms such as dehydration, or fever. Questions about symptoms related to viral infection may yield clues regarding infectious etiologies.

Characteristics

- Are your stools watery? Or are they more formed?
- Is there any blood in your stools?
- Are your stools mucousy, fatty, or containing pus?
- How many loose stools per day? ≥6?
- Are they large or small volume?

Exploring symptom characteristics further helps elucidate infectious etiology as well (viral vs. bacterial vs. noninfectious). These questions will also identify red flag features and severe symptoms. Bloody or purulent stools indicate a higher likelihood of bacterial infection [17].

History

- Have you had similar illnesses like this before?
- Did you take any antibiotics in the last 3 months?
- Have you done any traveling recently?
- Have you been hospitalized recently?
- Do any of your friends and family have a similar illness? Are you aware of any diarrhea outbreaks at work or school?
- Did you eat any food that could have made you ill?
- Have you recently started taking any new medications?
- What medications do you take?
- Do you have any drug or food allergies?
- What is your past medical history?

The history questions will elicit important information, such as antibiotic, travel, hospitalization, or other exposure histories. These will identify patients at risk for CDI or AAD, traveler's diarrhea, or food-borne illness. Certain chronic diseases are associated with diarrhea (e.g., IBD, irritable bowel syndrome, HIV), as are certain medications. Additionally, certain medications may require reassessment in terms of dosing if the diarrhea is severe enough to cause acute kidney injury (AKI). For example, significant diarrhea may affect the pharmacological effects of warfarin and the international normalized ratio (INR) should be rechecked in these cases.

Onset

- When did the diarrhea start?
- Was the onset gradual or abrupt?

It is important to know the duration of symptoms to categorize as acute, persistent, or chronic. Symptoms >7 days require referral to physician. Onset of illness is an important distinguishing feature.

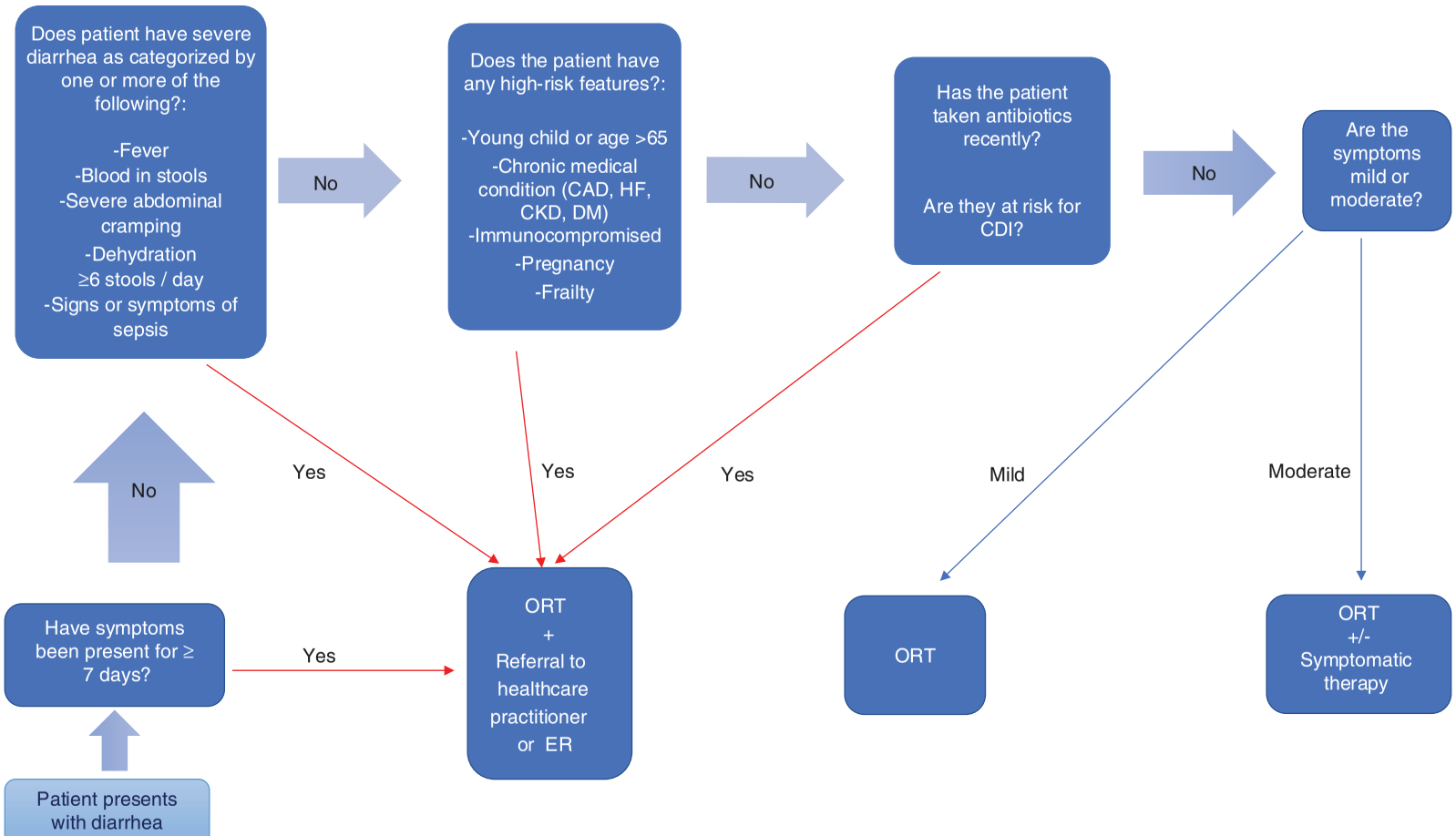


Fig. 7.1 Initial assessment and general management approach to diarrhea. CAD coronary artery disease, CDI *Clostridium difficile* infection, CKD chronic kidney disease, DM diabetes mellitus, ER emergency room, HF heart failure, ORT oral rehydration therapy

Location

- If abdominal cramping is present, explore the location of the cramps.

Aggravating Factors

- What makes your diarrhea worse?
- Have you noticed any foods that cause or worsen your diarrhea?
- Does the patient have baseline characteristics that predispose to diarrhea?
- Does the patient have any risk factors for diarrhea complications?

Make note if the patient has any chronic disease or food intolerances that could be contributing to their presentation. These patients will require further assessment by their family physician or specialist. See Red Flags section for high-risk patient-specific factors that warrant referral to the physician or the emergency department.

Remitting Factors (Treatment Options)

- Have you tried any pharmacologic or nonpharmacologic strategies?
- Did anything help?
- Did you experience any side effects? If yes, what are these?

It is important to know what the patient has tried, since this can help guide therapy.

Nonpharmacologic Measures

Maintaining fluid status/rehydration is the cornerstone of therapy for patients with diarrhea. For most adults with mild-to-moderate illness, oral rehydration therapy (ORT) can be delivered in the form of drinking adequate fluids, and by eating salty foods like saltine crackers and soups. Oral rehydration solution (ORS) should be considered for infants, the elderly, and anyone with substantial watery diarrhea [18]. If baseline weight is known, serial weight measurements can be an excellent way to gauge fluid losses [5]. In general, ORS is comprised of water, sugar, and electrolytes. ORS uses the sodium–glucose cotransporter in the small intestine to facilitate the absorption of water along with sodium and glucose. World Health Organization (WHO) endorses the use of ORS, and they have their own formulation. WHO reformulated their ORS in 2002 to have reduced osmolarity (245 vs. 311 mOsm/L). They have found that the reduced osmolarity ORS reduced stool output by 20%, reduced vomiting by 30%, and reduced the need for intravenous fluids (IVF) by 33%, when compared to the higher osmolarity solution [19]. There are several commercially available ORS, and there are also recipes for homemade solutions. Commercially available preparations are generally preferred to avoid mixing errors. Table 7.3 shows commercially available ORS options, as well as the WHO formulation. The following is a common recipe for a homemade ORS [16]:

- 2.5 mL (1/2 teaspoon) of salt
- 30 mL (2 tablespoons) of sugar
- 1 L safe drinking water.

Table 7.3 Oral rehydration solutions (ORS) [19–26]

ORS	Osmolarity (mmol/L)	Sodium (mmol/L)	Potassium (mmol/L)	Glucose (mmol/L)	Dextrose
WHO formula (2002)	245	75	20	75	
Gastrolyte®	240	60	20		90 mmol/L
Hydralyte®	245	45–60	20	81	
Pedialyte®, unflavored	250	45	20		25 g/L carbohydrate

WHO World Health Organization

Fluid replacement should account for initial losses, maintenance, and ongoing losses [17]. Online calculators are available [27]. For children, specific age-based recommendations are available from the Canadian Pediatric Society [28]. For patients with severe dehydration, IVF must be used initially to correct fluid deficits.

Pharmacologic Measures

If self-care measures are deemed appropriate, there are a number of pharmacological options that may be useful, as outlined in Table 7.4. It is important to rule out contraindications for antidiarrheal medications. Antimotility agents such as loperamide can precipitate toxic megacolon in patients with CDI, and are thus contraindicated for patients with suspected or known CDI. Loperamide can also prolong the duration and lead to more severe illness in patients with dysentery, so it should be avoided if any symptoms such as bloody or mucousy stools, fever, or severe abdominal cramping are present [17]. Antimotility agents can also mask fluid losses due to pooling of fluids in the intestines [29]. It should be noted that diarrhea that persists for more than 48 h after initiating loperamide merits medical attention [5]. Severe diarrhea should not be managed with loperamide or other symptomatic therapies on their own. See "Red Flags" section for characteristics of severe diarrhea that warrant referral to the physician or the emergency department. Antimicrobial therapy is not indicated for most cases of acute diarrhea, and must be used judiciously to prevent antimicrobial resistance and CDI. In cases of severe diarrheal illness, or in patients at high risk for complications, antibiotic therapy is often utilized [6].

Table 7.4 Medication options for diarrhea [9, 13, 17]

Drug	Dose (adults)	Comments
Loperamide	4 mg po × 1, then 2 mg as needed after each loose stool, maximum 16 mg/day	Antimotility agent Contraindicated in CDI
Diphenoxylate/atropine	5 mg (diphenoxylate) po 4×/day as needed	Antimotility agent Contraindicated in CDI Atropine is added to discourage misuse May be less effective than loperamide
Bismuth subsalicylate	524 mg (2 tablets) po every 30–60 min as needed up to 4.2 g/day)	Antisecretory and antimicrobial action Space from other medications
Attapulgite	1200–1500 mg po after each BM as needed, up to 8400 mg/day	Absorbs excess intestinal fluid Removed from US market due to lack of efficacy To be spaced from other medications

Red Flags

Red flags signal a need for referral to another healthcare practitioner, or the emergency room in some cases. Pharmacists play a key role in identifying patients who have red flag features.

Features of Severe Diarrhea [6]**:**

- Fever (≥38.5 °C).
- Bloody stools.
- Severe abdominal cramping.
- ≥6 loose stools in 24 h period.
- Symptoms lasting ≥7 days.
- Symptoms of dehydration (dark urine, reduced urine output, marked thirst, dizziness, dry mouth, decreased skin turgor, weight loss).

Any of the preceding symptoms indicate that the patient is experiencing severe diarrhea. Bacterial causes are more common in severe acute diarrhea compared to non-severe, especially when there is blood or pus in the stool, or if the patient is febrile. Further evaluation and management is required, and may include stool culture, stool for ova and parasites, *C. difficile* testing, abdominal X-ray, or endoscopy. The microbiology tests will help guide antibiotic therapy if required. Intravenous fluids are essential

if the patient is severely dehydrated. Worldwide, diarrhea causes 2.2 million deaths each year [30], largely due to dehydration.

High-Risk Patient-Specific Factors [1, 6]**:**

- Young children or age > 65
- Immunocompromised status
- Chronic illness such as cardiovascular disease, chronic kidney disease (CKD), or diabetes mellitus (DM1 or DM2)
- Frailty
- Pregnancy

These patients will be more sensitive to the physiologic changes that come with acute diarrhea, including dehydration, fluid shifts, and invasive infection. Closer monitoring is required, in addition to appropriate goal-directed therapies.

Monitoring and Follow-Up

The frequency and duration of follow-up should be guided by the severity of illness, presence or absence of dehydration symptoms, and presence of red flag features. These factors will determine what parameters to monitor as well. In all cases, patients should monitor how many bouts of diarrhea they are having per day, as well as stool characteristics such as consistency. The following cases will help illustrate possible follow-up plans:

- JZ is a 60-year-old male with history of hypertension, on ramipril and hydrochlorothiazide, presents to your pharmacy with diarrhea that started 36 h ago. He has had three loose stools in the past day, but feels well other than the diarrhea (afebrile, no dehydration symptoms). His current blood pressure is 120/85 mmHg (baseline ~130/90 mmHg). After you have decided on a treatment plan together, when would you want to follow-up?
  - Since JZ has no red flag features, he is appropriate for self-care. However, he is almost at the cutoff age, and he is also on two medications that could complicate his picture (ramipril increases his risk for AKI; hydrochlorothiazide increases the risk for hyponatremia, and both increase his risk for hypotension). It would be prudent to follow-up in the next 24–48 h to make sure his diarrhea is improving (e.g., number of loose stools per day), his blood pressure is not dropping, and he continues to be afebrile with no signs of dehydration, cramping, and blood in the stools. Additionally, inquire about any possible medications side effects (if pharmacological therapy was started), how much fluids he has been able to keep down, and whether he is able to eat normally.
- LV is a 30-year-old female with no past medical history and takes no regular medications. She has been having two loose stools per day for the past 2 days. She is afebrile, has no signs or symptoms of dehydration, but she does have mild abdominal cramping. Once you have decided on a treatment plan together, when would you want to follow-up with LV?
  - Since LV is young, with mild symptoms and no red flag features, it is appropriate to wait for a longer period of time to follow-up. It is reasonable to check in after 4 or 5 days to make sure that her diarrhea is resolving. In addition, it essential to check the number of loose stools/day, presence of any red flag features, and any side effects from medication if one was started.

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Constipation

8

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Chapter Objectives

1. Define constipation and identify its main causes.
2. Assess patients presenting with constipation.
3. Identify the red flags in patients presenting with constipation that prompt referral to healthcare practitioners.

Background

A patient comes to your pharmacy complaining of infrequent defection or constipation. What information do you need to conduct a proper assessment? To answer this question, pharmacists need to have a reasonable background about how constipation is defined and caused. In addition, gathering relevant patient-specific information spanning from symptom assessment to past medical history is essential to decide the proper course of action such as recommendation of a pharmacological or non-pharmacological therapy vs. referral for further assessment.

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Constipation is one of the common symptoms encountered by pharmacists in their day-to-day practice. It has been defined by the American College of Gastroenterology as an "unsatisfactory defecation and is characterized by infrequent stools, difficult stool passage, or both" [1]. According to the Canadian Digestive Health Foundation, one-fourth of Canadians experience symptoms of constipation to some degree, with 27% and 38% experiencing constipation within a 3-month and 12-month period, respectively. Constipation is more prevalent in women, older adults (>65 years), nonwhites and people with low economic status and sedentary lifestyle [2].

Etiology and Diagnosis

Determining the underlying cause of constipation is essential for proper assessment and subsequent management. Based on etiology, constipation is classified into primary and secondary. Primary constipation is not attributed to an identified cause and this includes functional (normal transit), slow transit, and obstructive constipation [3]. On the other hand, secondary constipation is the one attributed to a precipitating cause. Table 8.1 depicts secondary causes of constipation.

While assessing a patient presenting with constipation, clinicians need to determine if the patient actually has constipation. Acute or short-term constipation generally involves symptoms

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Table 8.1 Causes of secondary constipation

Drugs	Opioid analgesics Calcium channel blockers, e.g., verapamil Drugs with anticholinergic properties such as diphenhydramine, dimenhydrinate, tricyclic antidepressants Iron products, e.g., ferrous gluconate, sulfate and fumarate Calcium carbonate Aluminum-based antacids Levodopa/carbidopa Bismuth subsalicylate Cholestyramine Sucralfate
Disease	Dehydration Diabetes mellitus Hypothyroidism Cancer, e.g., colon cancer Gastrointestinal diseases, e.g., irritable bowel syndrome, intestinal obstruction Depression Anxiety Autonomic neuropathy Parkinson disease Spinal cord injuries
Other causes	Advanced age Lack of time and suppression of the urge to defecate Low-fiber, high-fat or high-sugar diet and reduced fluid intake

of reduced defecation frequency (fewer than three defecations per week or more than 4 days with no bowel movement), unsatisfactory evacuation, straining, and/or sitting in the toilet for a long time with no bowel movement that generally last for few days. On the other hand, functional chronic constipation is diagnosed if the patient has two or more of the following symptoms in more than a quarter of the defecations for at least 3 months (Rome III diagnostic criteria) [3, 4]:

- Low bowel movement frequency (less than 3 times per week)
- Straining
- Hard or lumpy stools
- Feeling of incomplete defecation
- Feeling of obstruction in the anorectal area
- Use of manual measures to facilitate defecation such as the use of digital evacuation and pelvic floor support

Symptom Assessment (SCHOLAR)

Proper assessment requires taking history regarding the characteristics of patients' constipation and the presence of any associated symptoms. This is in addition to identifying red flags that prompt referral to healthcare practitioners. A knowledge of the patient's medical and medication history allows proper selection and/or assessment of the appropriate pharmacological agents. In addition, it helps in identifying the possible precipitating factors for secondary constipation which could be attributed drugs or diseases. Figure 8.1 is a flow chart describing assessment of patients presenting with constipation in the pharmacy. The following questions are suggested in order to assess patients with constipation:

Symptoms and Characteristics

- Please describe your constipation. What do you mean by constipation?
- In addition to your constipation, did you experience any other symptoms? This might include nausea, vomiting, reduced appetite, rectal bleeding, abdominal pain ... etc.
- If you pass any stools, can you describe its consistency and color?
- Do you pass gas?
- Clarifying the characteristics and frequency of bowel movements and associated symptoms will help in determining if the patient actually has constipation (see etiology and diagnosis section) and identifying the presences of any red flags (see red flags section).

History and Onset

- How long have you been having constipation?
- Did this happen in the past? Was it different?
- Was there any recent change in your diet? Or fluid intake?
- Please describe your normal bowel habit. How many times per day or week do you normally have bowel movement?
- Was your constipation onset abrupt or gradual?

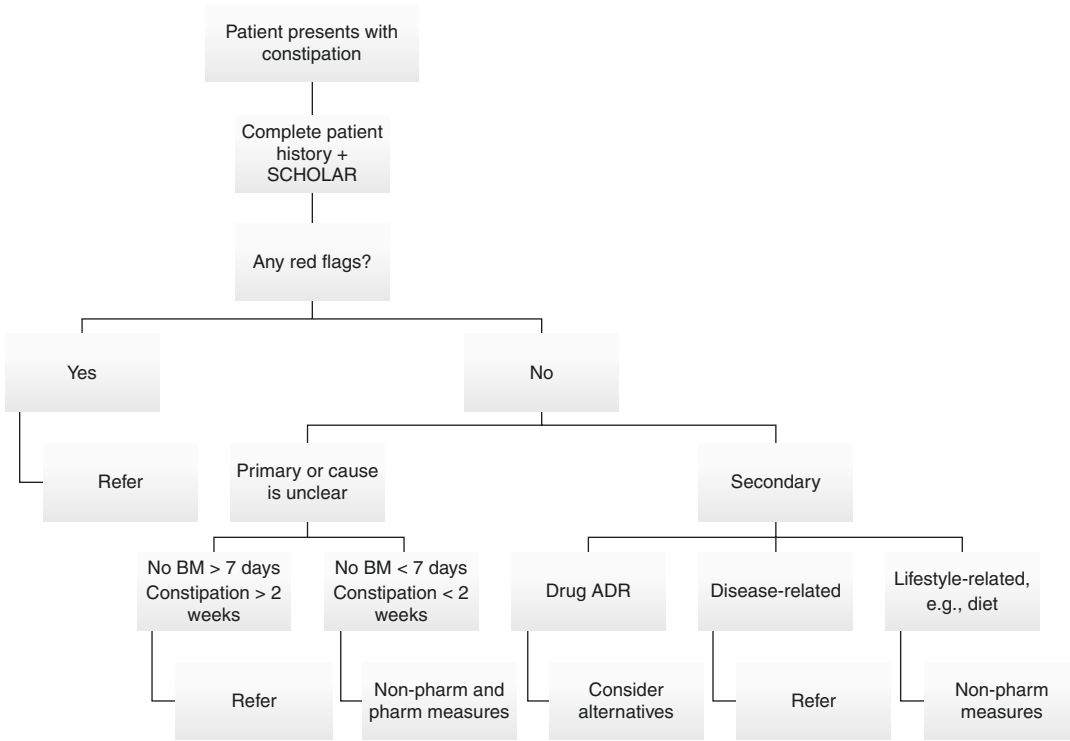


Fig. 8.1 Assessment algorithm for patients presenting with constipation in the pharmacy. ADR, adverse drug reaction; BM, bowel movement; SCHOLAR, **S**ymptoms, **C**haracteristics, **H**istory, **O**nset, **L**ocation, **A**ggravating and **R**emitting factors

Aggravating Factors

- What makes your constipation worse? A discussion about patient's triggers.
- Did you recently start on any medications, over-the-counter drugs, or herbals?
- Describe your diet and fluid intake.

Remitting Factors

- Have you tried anything for your constipation? Pharmacological and non-pharmacological.
- What worked and what did not work for you?

Several *non-pharmacological* measures that could be helpful in ameliorating constipation include the following:

- Increased fluid, fiber, prune, fruits, and vegetable intake.
- Maintain a regular bowel routine, e.g., going to the washroom at the same time every day.
- Avoid suppressing the urge to defecate.
- Exercise.

Multiple *pharmacological* measures are available for the management of constipation. Table 8.2 summarizes the currently available pharmacological choices for constipation. It is recommended that pharmacological options to be tried if non-pharmacological management was ineffective. First-line agents include bulk, osmotic, and stimulant laxatives. Stool softeners such as docusate sodium have been found to be no more effective than placebo and should not be recommended.

Table 8.2 Pharmacological options for constipation

Class	Agent (Adult Dose)	Comments
Bulk laxatives	Psyllium (3.4 g po once to three times daily)	To be taken with plenty of fluids Suitable for long-term use
Stool Softeners	Docusate sodium (100 mg po twice daily) Docusate calcium (240 mg po twice daily)	They are no more effective than placebo Not recommended
Osmotic laxatives	Polyethylene glycol 3350 (17 g po daily) Lactulose (15–30 ml po once or twice daily) Glycerin (1 adult suppository rectal when needed)	Suitable for long-term use An option for constipation secondary to opioids use
Stimulant laxatives	Senna 2 tablets po at bedtime Bisacodyl (10 mg suppository rectal when needed; 5–10 po daily)	An option for constipation secondary to opioids use
Others (second-line agents) to be tried if above agents are ineffective	Methylnaltrexone (6–18 mg subcutaneous injection every 2 days; dose depends on patient's weight)	For constipation secondary to opioids use
	Linaclotide (145 μg po daily)	For chronic constipation Expensive
	Prucalopride (1–2 mg po daily)	For chronic constipation Second line if other therapies fail
	Naloxegol (12.5–25 mg po daily)	For constipation secondary to opioids use

Patient-Specific Characteristics

In addition to assessing constipation and its associated symptoms, a knowledge of the patient's medical and medication history allows proper selection and/or assessment of the appropriate pharmacological agents. In addition, it helps in identifying the possible precipitating factors for secondary constipation (see Table 8.1). The following examples illustrate how patient-specific characteristics are essential in constipation assessment:

- *Age:* Individuals older than 65 years are at higher risk of developing constipation than younger ones. This is because they are more likely to have multiple comorbidities and multiple drugs.
- *Pregnancy status:* Increased pressure on the abdomen, combined with hormonal changes and possible calcium intake, increases the propensity to constipation in pregnant women. Non-pharmacological measures should be tried first. If constipation persists, bulk laxatives could be tried followed by osmotic laxatives if needed.
- *Past medical history:* Identifying patient's comorbidities will help in recognizing the possible causes of secondary constipation. Ideally, controlling the underlying conditions, if possible, could resolve constipation. The use of laxatives in the interim is recommended.
- *Medication history:* Identifying patient's current medications will help recognize the possibility of drug-induced constipation (see Table 8.1). It is more important to confirm the temporal relation between drug initiation and symptom onset. If one of the patient's medications is the culprit, alternative therapy could be considered, if possible.
- *Diet:* Low-fiber, high-fat, or high-sugar diet and reduced fluid intake increase the propensity for constipation. Patients should be advised to increase their fiber and fluid intake.

Red Flags

It is very important to determine if the patient's constipation could be caused by an underlying medical condition. Presence of any of the following red flags prompts referral to a healthcare practitioner:

- Blood in stool or rectal bleeding
- Recent surgery (especially abdominal surgery)
- Family history of colon cancer
- Continuous abdominal pain
- Constipation for more than 2 weeks or no defecation for more than 7 days
- Presence of any associated symptoms indicating a more serious illness, e.g., fever, altered mental status, signs of severe dehydration, persistent vomiting
- Anemia
- Unexplained weight loss

Additional Assessment Considerations

Further assessment for patients with red flags is recommended. Assessment considerations include, but are not limited to, the following:

- Physical examination of the abdomen and rectal area
- Laboratory investigations to determine the secondary causes of constipation such as thyroid function tests, electrolytes, complete blood count, and test for occult blood
- Colonoscopy or sigmoidoscopy

Follow-Up and Monitoring

The goals of therapy are to ameliorate constipation through achieving satisfactory optimal defecation frequency, avoid complications such as hemorrhoids secondary to straining, and avoid adverse reactions of drug therapy. Achieving "optimal" defecation frequency goal should be individualized according to the patient's normal bowel habits. For examples, for patients used to have a bowel movement daily, it is reasonable to target a daily bowel movement. On the other hand, it is reasonable to target three defecations per week for patients used to have 3–4 defecations per week.

At follow-up assessment, patients deemed suitable for non-pharmacological and/or pharmacological measures should be asked if their constipation persists. Presence of constipation for more than 2 weeks or no bowel movements for more than 7 days should prompt referral to healthcare practitioners. A laxative is considered ineffective if there is no response following a trial period of 2–4 weeks at the recommended dose. In addition to checking for symptom control, pharmacists need to monitor if the patient experiences adverse reactions to pharmacological management. Adverse reactions include, but are not limited to, abdominal cramping, bloating, flatulence, diarrhea, and nausea.

Clinical Pearls

- Pharmacists play an important role in identifying red flags in patients presenting with constipation.
- Assessment of patients presenting with constipation involves assessment of the characteristics and history of patients' constipation and the presence of any associated symptoms.
- Pharmacists need to assess for medication-induced constipation and determine the need for alternative therapies.

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Heartburn

9

Mark Makowsky

Chapter Objectives

1. Describe the epidemiology, etiology, risk factors, and pathophysiology of heartburn.
2. Assess adult patients presenting with heartburn in the community pharmacy setting.
3. Identify alarm features in adults presenting with heartburn that prompt referral to a physician or emergency department.
4. Conduct follow-up assessment of a patient on long-term proton pump inhibitor (PPI) therapy with a view toward reducing the dose or stopping the PPI altogether.

Background

A patient comes into the pharmacy requesting your advice for treatment of heartburn symptoms. What is the process for assessment and determining if self-treatment is appropriate? In order to answer this question, pharmacists must have a fundamental knowledge of the common underlying causes of heartburn, potential differential diagnoses, and be able to gather relevant patient-specific information in order to determine if the patient can safely pursue self-care or requires referral to a physician. Guideline recommendations state that a presumptive diagnosis of gastroesophageal reflux disease (GERD) can be established in the setting of typical heartburn and regurgitation symptoms and that empiric therapy can be initiated in this context without further workup [1]. Therefore, pharmacists are uniquely placed to play a role in the evaluation of patients with heartburn symptoms and direct individuals to effective over-the-counter (OTC) therapies such as antacids, alginates, histamine 2 receptor blockers (H2RA), and proton pump inhibitors (PPI) for self-treatment [2–5].

Classification of Upper Gastrointestinal (GI) Symptoms: GERD Versus Dyspepsia

Heartburn, defined as a burning sensation in the retrosternal area (behind the breastbone), and *regurgitation*, defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx, are the primary symptoms of *gastroesophageal reflux disease* (GERD) [6]. GERD is defined by consensus as "A condition that develops when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications" [6]. Notably, some degree of gastroesophageal reflux, or movement of gastric contents into the esophagus, is physiologic [7]. Heartburn is considered troublesome if mild

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symptoms occur 2 or more days per week, or moderate/severe symptoms occur more than 1 day per week [6]. In situations where endoscopic evaluation is appropriate, GERD can be further classified as nonerosive reflux disease (i.e., the presence of symptoms without visible erosions) or erosive reflux disease (i.e., symptoms and erosions are present on endoscopy; aka erosive esophagitis) [1].

In addition to heartburn and regurgitation, GERD may manifest with other "atypical" or "alarm" symptoms, which should prompt referral to a physician or an emergency room for further investigation depending on the severity of the condition (Table 9.1). For example, chest pain may be a symptom of GERD and the pain may be cardiac or noncardiac in nature. It is essential to distinguish cardiac from noncardiac chest pain before considering GERD as a cause of chest pain [1]. Dysphagia, chronic cough, asthma, and laryngitis are possible so-called extra-esophageal symptoms [1]. GERD may also present with atypical symptoms including dyspepsia, epigastric pain, nausea, bloating, and belching, but these symptoms also overlap with other conditions [1]. The main complications of GERD include erosive esophagitis, Barrett's esophagus, esophageal strictures, esophageal carcinoma, and extra-esophageal symptoms as described above [1].

The presence of alarm features may suggest the presence of complications or malignancy [1]. As shown in Table 9.1 the main alarm symptoms are:

- Vomiting (persistent)
- Evidence of GI bleeding, (e.g., hematemesis, melena, hematochezia, occult blood in stool)
- New onset dyspepsia in patients ≥50 years of age
- Anemia
- Anorexia (loss of appetite)
- Weight loss (unexplained)
- Dysphagia (difficulty swallowing) or odynophagia (pain when swallowing)
- Gastrointestinal cancer in a first-degree relative

Patients presenting to family physicians with upper GI symptoms, making symptoms-based diagnosis in these patients difficult in practice [10, 11]. While heartburn is typically indicative of GERD, there is considerable overlap with dyspepsia symptoms. *Dyspepsia* is defined as predominant epigastric pain for at least 1 month [9]. Dyspepsia may be associated with other GI symptoms such as epigastric fullness, nausea, vomiting or heartburn, provided epigastric pain is the patient's primary concern [9]. Upon presentation and in the absence of investigation, patients may be labeled as having "uninvestigated" dyspepsia. Approximately 40% of patients with uninves-

Table 9.1 Gastroesophageal reflux disease: typical symptoms, atypical symptoms, and alarm features that require referral to a physician

Typical symptoms	Atypical and/or nonspecific symptoms	Alarm symptoms
Heartburn (a burning sensation in the retrosternal area (i.e., behind the breastbone)	Chest pain Nausea Belching Epigastric pain Respiratory symptoms (recurrent cough, hoarseness, wheeze, rhinosinusitis)	Persistent vomiting Gastrointestinal bleeding (hematemesis, melena) Iron-deficiency anemia Involuntary weight loss (>5%) Difficult/painful swallowing (dysphagia, odynophagia)
Regurgitation (the perception of flow of refluxed gastric content into the mouth or hypopharynx)	Choking attacks, especially at night Nocturnal awakening	Epigastric mass Family history of esophageal or gastric cancer New onset of symptoms ≥50 years of age

Adapted from Boardman 2015 [4], Armstrong 2016 [5], and Hunt 2017 [8], ACG/CAG Dyspepsia guidelines [9]

tigated dyspepsia have an underlying organic cause for their symptoms (e.g., peptic ulcer disease, reflux esophagitis, gastroesophageal malignancy, drug-induced dyspepsia, biliary pain), while up to 60% have "functional" dyspepsia, that is, dyspeptic symptoms with no underlying organic cause on diagnostic evaluation [12]. It has been generally accepted that endoscopy is not routinely needed in those with a clinical diagnosis of functional dyspepsia [13]. Current dyspepsia clinical practice guidelines conditionally suggest endoscopy to exclude upper GI malignancy in dyspepsia patients age 60 or over based on very low-quality evidence [9]. In dyspepsia patients under the age of 60, they suggest endoscopy is not necessary to investigate alarm features (conditional recommendation, moderate quality of evidence) and rather suggest noninvasive *Helicobacter pylori* testing in these patients (strong recommendation, high-quality evidence). Further, in those who are *H. pylori* negative or remain symptomatic after *H. pylori* eradication, they strongly recommend empirical physician-supervised empirical PPI therapy based on high-quality evidence. Others have suggested in areas with known local prevalence of *H. pylori* < 20%, proceeding straight to empiric PPI therapy in place of *H. pylori* testing as the preferred approach [14].

Epidemiology

GERD symptoms are prevalent worldwide. For example, a recent systematic review of 28 studies of GERD prevalence suggested that GERD defined as at least weekly heartburn and/or regurgitation is present in 18–28% of Americans and between 9% and 26% of Europeans [15]. The Canadian Consensus Conference Guideline states that "GERD is the most prevalent acid related disorder in Canada" (Level II-1, A evidence) [16]. This is primarily based on a population survey of 1000 Canadians where 17% reported heartburn in the previous 3 months; and 13% experiences moderate/severe upper GI symptoms weekly [17]. Clinically troublesome heartburn is seen in about 6% of the American population [18].

Etiology and Risk Factors

The development of GERD reflects an imbalance between aggressive and physiological defense mechanisms in the gastrointestinal tract [19]. The main causes and risk factors are listed in Table 9.2. Esophagitis, a complication of GERD,

Table 9.2 Possible causes of GERD [8, 20, 21]

Drug causes	Decrease lower esophageal sphincter pressure Anticholinergics Alpha agonists Beta agonists Calcium channel blockers Estrogen Opioids (e.g., morphine) Theophylline Nitrates (e.g., isosorbide mononitrate) Benzodiazepines (e.g., diazepam) Clomipramine Barbiturates Direct irritation of mucosa Bisphosphonates Iron (e.g., ferrous sulfate) Potassium supplements Ascorbic acid Erythromycin, tetracycline, doxycycline, clindamycin Quinidine Chemotherapy (e.g., paclitaxel) Direct irritation of mucosa and COX inhibition Aspirin NSAIDS Corticosteroids
Disease causes	Mechanical or functional impairment of the esophagogastric junction, e.g., hiatus hernia Obesity Pregnancy
Other causes	Smoking Alcohol Foods High fat content, chocolate, peppermint (lower LES pressure) Spices, onions, citrus juice, coffee (direct mucosal irritation) Cola, beer, milk (stimulate acid secretion) Body position Bending over, lying down

NSAID nonsteroidal anti-inflammatory drug, *COX* cyclooxygenase, *LES* lower esophageal sphincter, *GERD* gastroesophageal reflux disease

occurs when refluxed gastric acid and pepsin cause necrosis of the esophageal mucosa causing erosions and ulcers [22].

The two main pathophysiologic mechanisms of GERD are gastroesophageal junction incompetence and impaired esophageal acid clearance [19]. Gastroesophageal junction incompetence may be caused by several mechanisms including spontaneous and transient relaxation not associated with swallowing, low-resting lower esophageal sphincter (LES) pressure, anatomic disruption of the gastroesophageal junction (e.g., hiatus hernia), and transient increase in intraabdominal pressure (e.g., straining, pregnancy) [22]. Improper esophageal clearance of gastric fluid may be due to ineffective esophageal motility, or retrograde flow associated with hiatus hernia; and diminished salivation or salivary neutralizing capacity [19]. While the extent of symptoms and mucosal injury is proportional to the frequency of reflux events, the duration of mucosal acidification, and the caustic potency of refluxed fluid, gastric acid hypersecretion is not usually a dominant factor in GERD [22].

Several factors may exacerbate or trigger GERD symptoms [19, 22]:

- Lifestyle factors: Abdominal obesity, eating large meals, alcohol consumption, smoking, caffeine, stress.
- Pregnancy, gastric hypersecretory states, delayed gastric emptying, disruption of esophageal peristalsis.
- Certain foods (fatty or fried foods, coffee/tea or other caffeinated beverages, spicy foods, acidic foods [e.g., citrus, tomatoes, onions], or others [chocolate, mint]).
- Bending over or lying down after eating, wearing tight-fitting clothing.

There are several risk factors for GERD. They include being overweight or obese, diet, pregnancy, smoking, other medical conditions such as Crohn's disease and hypothyroidism, and use of medications [20, 21].

Categorization and Management of Presumptive GERD

Numerous clinical practice guidelines exist regarding the management of GERD [1, 8, 16, 23, 24] and several have been specifically tailored to address the community pharmacist management of heartburn/GERD [2–5, 13, 25–30]. The various lifestyle and pharmacologic options for the management of heartburn and GERD are shown in Table 9.3 [31, 32].

Classically, symptom severity, frequency, and duration have been important in determining whether self-treatment is appropriate or referral for prescription PPI therapy should be pursued. Classically, GERD symptoms have been typically characterized as mild or moderate/severe [16]:

- *Mild GERD* is characterized by infrequent reflux symptoms (<3 times per week), of low intensity (e.g., 1–3 out of 10) and short duration (e.g., <3 months), and with minimal long-term effect on activities of daily living or quality of life.
- *Moderate or severe GERD* is characterized by more frequent, intense, or prolonged symptoms (e.g., daily attacks of reflux pain, symptoms present for >3 months, pain intensity 7–10 out of 10, or symptoms that interfere with daily activities and occur at night).

In most algorithms, mild/moderate symptoms are deemed appropriate for self-treatment, while those with severe heartburn were to be referred to their family physician for prescription PPI therapy. Patients with severe symptoms may have esophageal erosions characteristic of Barrett's esophagus. However, the relationship between presenting symptomatic frequency or severity and severity of esophageal injury is weak (i.e., those with less severe symptoms may have these conditions as well) [5].

In new approaches that take into consideration the availability of OTC PPI therapy, heartburn is

classified as either occasional (i.e., episodic) or frequent. For example, the World Gastroenterology Organization (WGO) guidelines for community-based management of gastrointestinal conditions classify heartburn as being episodic when heartburn is mild or moderate, but infrequent. Frequent heartburn is 2 or more days per week [5, 24]. In this approach, referral is suggested if symptoms have lasted for 3 months, or when severe or nocturnal heartburn is present [24]. The WGO guidelines suggest use of antacids, alginates, or OTC H2RA for those with mild or moderate episodic heartburn (i.e., <1x/week) and OTC PPI therapy for those with frequent heartburn (Fig. 9.1) [24]. In Canada, OTC PPI therapy with omeprazole or esomeprazole are indicated for the treatment of frequent heartburn only [33, 34]. While some are conservative and suggest referral and no OTC PPI therapy when symptoms have lasted >3 months, are severe or nocturnal [24, 26], others suggest that an OTC PPI is appropriate but also to concurrently refer patients with severe GERD symptoms [2]. Most recent pharmacist-specific algorithms recommend self-treatment with OTC PPI trial for 2–4 weeks and no referral for those with frequent or bothersome symptoms [4].

Table 9.3 Nonpharmacologic and pharmacologic management strategies for gastroesophageal reflux disease

Nonpharmacologic strategies [31]	Examples
Lifestyle and dietary modification	Weight loss for those who are overweight
	Elevate the head of the bed by 10–20 cm particularly if nocturnal symptoms are present
	Elimination of dietary triggers in those who note correlation with GERD symptoms and experience symptomatic improvement
	Avoid eating up to 3 h before bedtime
	Avoid lying down after meals
	Stop smoking
	Avoid alcohol
	Avoiding tight fitting clothing
Pharmacologic choices [32]	Generic name and adult dose
Antacids	Magnesium–aluminum hydroxide (e.g., Maalox®, Mylanta®); see label instructions for dosing Calcium carbonate 200–400 mg PRN (max 2 g elemental calcium in 24 h)
Alginates	Sodium alginate (e.g., Gaviscon® 2–4 tsp. QID) Sucralfate 1 g TID or QID
Histamine 2 receptor blockers	Ranitidine (OTC: 75 mg daily) 150 mg BID Famotidine (OTC: 10 mg daily) 20 mg BID Nizatidine 150 mg BID Cimetidine 600 mg BID
Proton pump inhibitors[a]	Esomeprazole (OTC: 20 mg daily x 2 weeks) 40 mg daily Omeprazole 20 mg daily (OTC: 20 mg daily x 2 weeks) 20 mg daily Pantoprazole 40 mg daily Rabeprazole 20 mg daily Lansoprazole 30 mg daily Dexlansoprazole 60 mg daily
Other	Bismuth subsalicylate (Pepto Bismol®) 30 mL (2 tablets) q30–60 min PRN (max 8 doses/day)

Note: There is limited evidence to support the effectiveness of lifestyle changes aside from weight loss and elevating the head of the bed

GERD gastroesophageal reflux disease, *PRN* as required, *OTC* over the counter

[a]Duration of therapy for physician-supervised therapy is 4–8 weeks

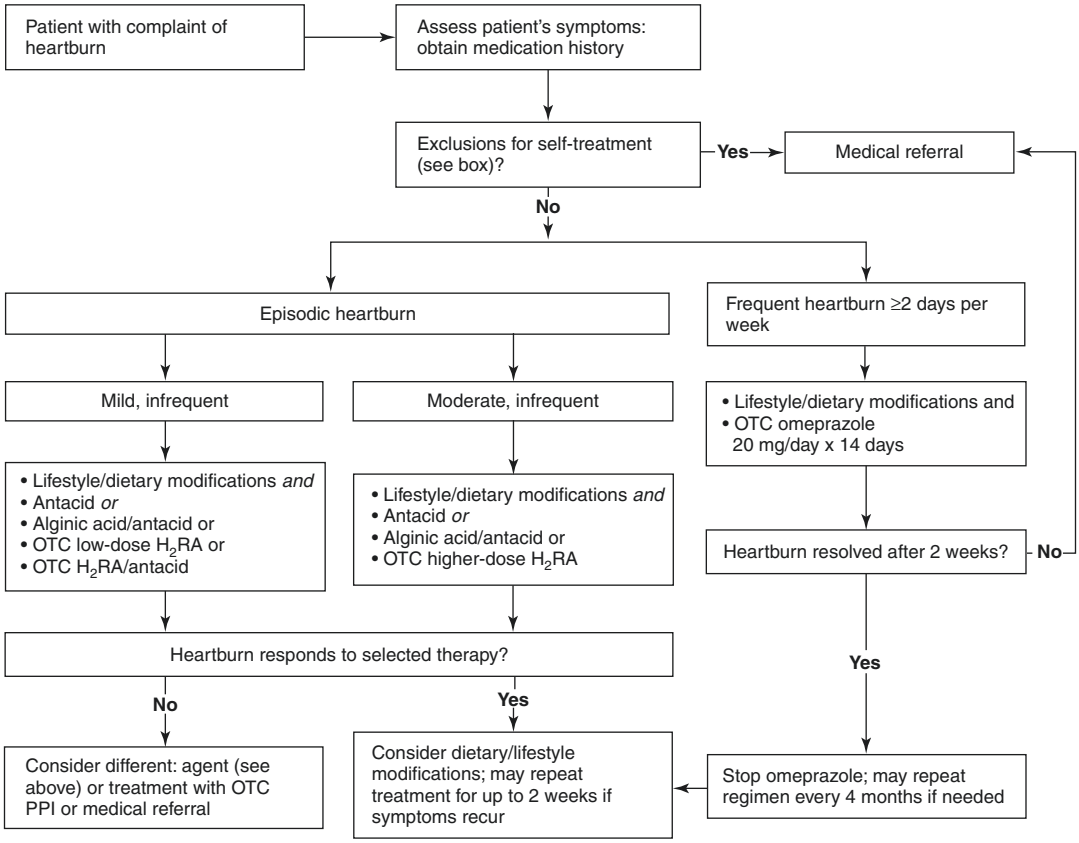


Fig. 9.1 Self-care algorithms for heartburn [24]. OTC over the counter, H2RA histamine 2 receptor antagonist, PPI proton pump inhibitor. (Reprinted by permission from Wolters Kluwer Health. Hunt et al. [24])

Diagnosis

The most useful tool in diagnosis of GERD is the history [16, 35]. The diagnosis of GERD can often be based on clinical symptoms alone in patients with classic symptoms of heartburn and/or regurgitation [6]. It is commonly reported that the presence of heartburn or acid regurgitation has a high specificity (89% and 95%, respectively), but a low sensitivity (38% and 6%) to diagnose GERD [35]. A more recent systematic review of seven studies found the sensitivity of heartburn and regurgitation for the presence of erosive esophagitis to be 30–76% and specificity from 62% to 96% [36]. Upper gastroesophageal endoscopy is not required to make a diagnosis of GERD. However, it can detect esophageal manifestations of GERD and identify upper GI tract malignancy. There are usually no physical signs of GERD and the role of physical assessment in the evaluation of heartburn, regurgitation, or GERD is limited to evaluation and inspection to exclude other medical problems such as cardiac disease, asthma, or cancer [8].

While some have suggested that a symptomatic response to proton pump inhibitor therapy can be used as diagnostic tool, and this is commonly done in practice, this is not a diagnostic criterion for GERD [8, 37, 38]. The American College of Gastroenterology GERD guidelines suggest empiric PPI therapy is a reasonable approach to confirm GERD when it is suspected in patients with typical symptoms [1]. However, a meta-analysis suggested that an empiric trial of

PPI therapy had a 78% sensitivity and 54% specificity for predicting a diagnosis of GERD [38].

Further investigations that may be requested by a physician to evaluate heartburn or GERD include endoscopy, and esophageal pH monitoring. Barium radiographs should not be performed to diagnose GERD [1]. Endoscopy is recommended in patients with alarm symptoms or non-responders. Ambulatory 24 h pH monitoring and impedance monitoring are indicated in patients whose atypical reflux symptoms call a GERD diagnosis into question, in those who fail standard medical therapy but have normal endoscopy, and as preoperative evaluation before anti-reflux surgery [39]. H. pylori screening is not recommended in GERD. Eradication of H. pylori infection is not routinely required as part of anti-reflux therapy [1]. However, H. pylori testing is carried out when peptic ulcer disease is suspected.

The differential diagnosis for GERD includes cardiac disease, peptic ulcer disease, infectious esophagitis (e.g., Candida, herpes simplex), pill esophagitis, eosinophilic esophagitis, Schatzki ring, dysphagia caused by esophageal motility disorder, esophageal obstruction, esophageal cancer, reflux hypersensitivity, dyspepsia (e.g., functional dyspepsia), and biliary colic [8, 22].

Initial Assessment of New Self-Diagnosed Heartburn Symptoms in Adults

As GERD management has been recognized as an area of pharmacist impact, and with the availability of OTC proton pump inhibitor therapy for the short-term (2 weeks) management of frequent heartburn, consensus treatment algorithms [2, 4, 13, 25, 29] and documentation flowsheets [26] have been created to guide pharmacist assessment of heartburn symptoms in adults (Fig. 9.2). While each is different, all share commonalities in their approach to the patient presenting with new heartburn symptoms.

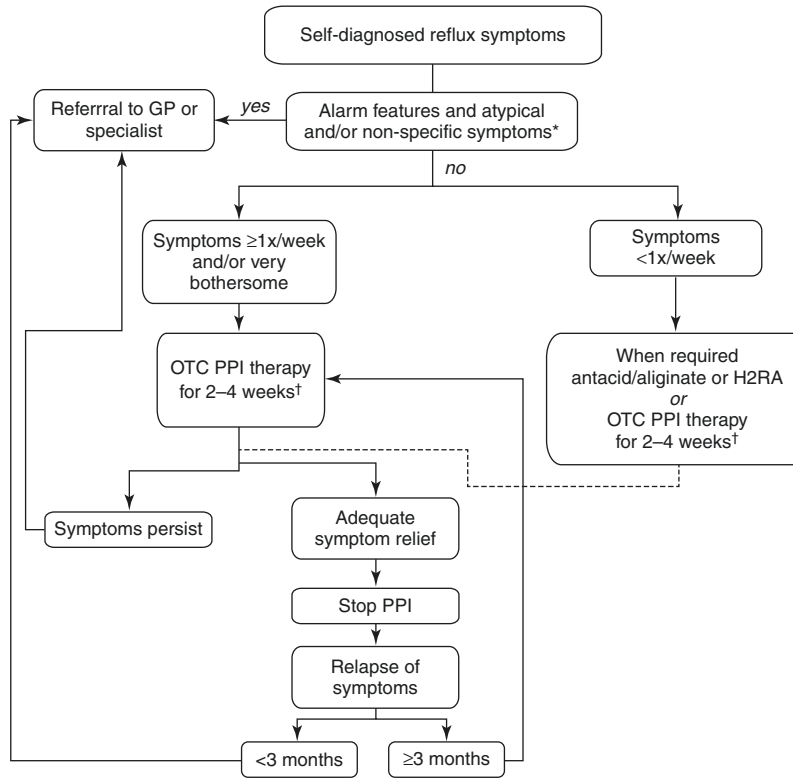


Fig. 9.2 Algorithm for pharmacy-based management of typical reflux symptoms [4]. GP general practitioner, OTC over the counter, H2RA histamine 2 receptor antagonist, PPI proton pump inhibitor. (Reprinted by permission from Taylor and Francis. Boardman et al. [3])

- *Establish the diagnosis:* Confirming the indication for therapy by enquiring about the nature of the patient's symptoms [2]. Enquire if the patient has been previously diagnosed with GERD by a physician. Remember, while many patients may have other upper GI complaints, in GERD, heartburn and regurgitation will be the predominant symptom.
- *Determine whether referral to a physician is required:* Referral is required in patients with alarm features, those with a familial or personal history of gastrointestinal cancer, age of onset of symptoms at age ≥ 55, or in situations where patients have been nonresponsive to prior attempts at self-treatment with OTC H2RA or PPIs. If the patient's dominant symptoms are consistent with heartburn and regurgitation and the patient does not have any alarm or atypical symptoms, the community pharmacist can make a presumptive diagnosis of GERD.
- *Assess medical and medication history*: To assess drug-induced causes of reflux and assess the appropriateness of treatment alternatives.
- *Establish symptom frequency and severity:* Enquire about the characteristics and onset of symptoms to determine if patients have episodic or frequent heartburn. While some treatment algorithms suggest OTC PPI therapy for patients with episodic heartburn [2, 4], it is recommended to treat episodic heartburn initially with antacids, alginates, or H2RA and reserve OTC PPI therapy for patients with frequent heartburn [4, 24, 33, 34].

Table 9.4 depicts a list of potential questions that will aid in proper assessment of adult patients with heartburn symptoms.

Symptoms and Alarm Features

The pharmacist should start by asking the patient to describe his or her symptoms and listen for cues regarding typical, atypical, and alarm symptoms. When evaluating heartburn symptoms, it is essential to differentiate scenarios where patients are experiencing new undiagnosed symptoms, or whether they have physician-diagnosed GERD. Among the first questions, the pharmacist should enquire about atypical and alarm symptoms (as shown in Table 9.1) to identify any red flags and if any are present, the patient should be referred to his/her physician. Patients with atypical or extraesophageal symptoms such as chest pain, chronic cough, hoarseness, sore throat, shortness of breath, and wheezing should be referred to their physician for further workup [5].

Reflux-like symptoms can occur in other GI conditions (e.g., functional dyspepsia) and the treatment options are different [5]. If the description of symptoms is more consistent with dyspepsia, then peptic ulcer disease, GI cancer, and functional dyspepsia are part of the differential diagnosis. In this case, referral to the family physician for H. pylori testing or a supervised empiric trial of 4–8 weeks of proton pump inhibitor therapy are among the options as discussed above [9]. As part of the process, the pharmacist should be aware of other possible causes of dyspepsia, including cardiac or hepatobiliary causes of epigastric pain.

History

Gathering a medical and medication history is necessary in patients with heartburn symptoms to identify potential drug-induced dyspepsia and assess the appropriateness of the different therapeutic options. The use of chronic NSAID or ASA therapy is a well-known risk factor for peptic ulcer disease and may suggest that dyspeptic symptoms are related to peptic ulcer disease rather than GERD. Several other classes of drugs are known to cause dyspepsia and esophageal complications and these should be ruled out (see Table 9.2). Additionally, there are several clinically important drug interactions that pharmacists should aim to avoid when suggesting therapy for GERD. For example, an acidic stomach environment is required for absorption of specific antiretroviral drugs and in these situations proton pump inhibitor therapy may be absolutely contraindicated [40]. Another notable drug interaction

Table 9.4 Potential questions to assess patients presenting with heartburn symptoms [4, 5, 26]

Step	Question	Notes
Establish the diagnosis	What is the nature of your symptoms? Have you been previously diagnosed with GERD by a physician?	Typical symptoms of heartburn and regurgitation suggest a presumptive diagnosis of GERD. Heartburn symptoms are substernal in location and may travel up the esophagus to the pharynx. Atypical symptoms prompt referral Predominant epigastric pain symptoms just below the ribs in the upper central area of the abdomen (i.e., dyspepsia) require referral
Rule out referral for alarm symptoms	Are you experiencing difficulty swallowing or having pain when you swallow? Do you have any signs of internal GI bleeding (e.g., black tarry stools, vomiting blood) Are you over the age of 50 and are these new symptoms? Have you lost a significant amount of weight (i.e., >5%) without trying? Are you vomiting? Do you have a history of anemia, or signs of anemia? Do you have a first-degree relative with a history of gastric and or esophageal cancer?	Presence of alarm features prompts referral
Medical and medication history	For females: Are you pregnant? What medications are you currently taking? Are you taking medications which could be causing the symptoms? Are you on chronic NSAID or ASA therapy? Medical history? What other medical conditions has your doctor diagnosed?	Self-management with antacids is appropriate in pregnancy. Therapy should be supervised by a physician.
Characteristics and onset	How often do you get (heartburn) symptoms? On a scale of 1–10, how severe is your heartburn? How long do your symptoms last? Do your symptoms happen at night? Do your symptoms affect your daily activities, work productivity? How long have you been having (heartburn) symptoms? (i.e., when did your symptoms start) Is this your first episode of heartburn, or is this a relapse of symptoms? Have you ever had an endoscopy before?	*Episodic* heartburn is mild or moderate, but infrequent and may be treated with antacids, alginates, H2RA, and OTC PPI *Frequent* heartburn is 2 or more days per week, treated with PPI
Aggravating/ remitting factors	Have you tried any lifestyle changes or medications that have made your symptoms better or worse?	Retreatment is appropriate for patients whose symptoms recur more than 3 months after stopping previously effective over the counter proton pump inhibitor therapy Patients with refractory symptoms require referral

GERD gastroesophageal reflux disease, *PPI* proton pump inhibitor, *OTC* over the counter; *GI* gastrointestinal

of PPIs is the interaction of omeprazole and clopidogrel post cardiac stent [41]. Several classes of medications (e.g., fluoroquinolones, tetracyclines) are known to have clinically significant interactions with antacids [42].

Assessment of Patients with Recurrent Symptoms

Clarifying if the patient is experiencing a first episode or recurrence of heartburn symptoms helps the pharmacist orient themselves during the patient assessment and in the determination of whether or not repeated self-treatment is appropriate. The assessment of patients with recurrent symptoms is consistent with the initial assessment of new patients described above. However, the pharmacist must gather more history regarding the resolution of symptoms and previous treatment in order to make appropriate recommendations.

Patients who have refractory symptoms (i.e., persistent symptoms despite appropriate treatment) should be referred to a physician [4, 33]. This may relate to incorrect diagnosis, nonadherence, or inadequate acid suppression. Patients have initiated OTC PPI therapy and had a resolution of GERD symptoms but experience a recurrence >7 days but less than 3 months despite a trial of over-the-counter PPI therapy should also be referred to their family physician [4]. If symptoms recur more than 3 months after stopping previously effective over-the-counter PPI, retreatment is appropriate [4]. A history of a previous endoscopy likely indicates an established history of GI disease and in this case self-treatment may not be appropriate.

Assessment and Management of Heartburn in Pregnancy

Heartburn is common in pregnancy, with a reported incidence between 17% and 45% [43]. It is typically more common in the latter stages of pregnancy. For example, studies have found the prevalence to increase from 22% in the first trimester, to 39% in the second trimester, and 72% in the third trimester [44]. The cause of heartburn is multifactorial. Pregnancy likely aggravates GERD due to a decrease in lower esophageal sphincter pressure caused by changes in hormonal status, displacement of the lower esophageal sphincter into the thoracic cavity and increased intraabdominal pressure [43, 45]. Heartburn usually resolves after delivery [46].

Pharmacist-tailored OTC PPI treatment algorithms generally do not address management of heartburn in pregnancy [2, 4, 13], but guidelines recommend that self-treatment is not appropriate [24, 25]. Some recommend referral to a physician [25], while product monographs for OTC PPI available in Canada suggest pregnant or breastfeeding females talk to their doctor or pharmacist before a trial of therapy [33, 34].

The evidence for lifestyle and pharmacologic management of heartburn in pregnancy has been summarized elsewhere [43, 47]. However, establishing the efficacy of interventions in this context has been limited by a lack of trials in this population. A step-up approach beginning with lifestyle and dietary modification, followed by antacids, alginates, or sucralfate (FDA Category B), then H2RA, and finally PPI is recommended [8, 48]. Antacids, alginates are safe in pregnancy and breastfeeding. Calcium-based antacids are preferred because adverse effects are rare and they have been shown to be beneficial in the prevention of hypertension and preeclampsia and reduce the composite outcome of maternal death or serious morbidity [49]. There is a lack of clinical trial evidence regarding the efficacy of H2RA in heartburn in pregnancy [43]. Despite this, ranitidine can be combined with antacids if antacids alone are insufficient. Ranitidine is FDA Category B and is considered by experts as safe in pregnancy [46, 50]. There is limited evidence for proton pump inhibitors in pregnancy. A group of experts made a strong recommendation based on 3-star quality evidence that there is no contraindication for the use of Category B OTC PPIs for heartburn during pregnancy [27]. The FDA considers omeprazole as Category C, while all other PPIs are category B. Despite this, currently available

data suggest that omeprazole is not teratogenic in humans and recognize that omeprazole has the largest reported safety experience as it has been used in the largest number of treated patients [51]. Based on moderate level evidence, the ACG 2013 guidelines make a conditional recommendation that PPIs are safe in pregnant patients if clinically indicated [1].

Follow-Up Assessment

Newly Initiated Therapy for Heartburn

Follow-up assessment of patients initiated on OTC treatments for heartburn is not mandatory in all situations as the goal of self-treatment is to have the patient become symptom-free. If patients are started on OTC PPI, inform them to call back to the pharmacy/consult a physician if symptoms have not resolved in 2–4 weeks' time, as this suggests the presence of peptic ulcer disease or erosive esophagitis. A potential risk of continuing OTC PPI beyond 2 weeks is delaying presentation for early esophageal cancer [27]. Return of symptoms after a period of months after successful therapy may be an indication for another course of therapy [4]. Referral to a physician is suggested if:

- Patients do not respond to initial OTC PPI therapy.
- Individuals have persistent (>1 month) or recurrent symptoms after use of an OTC PPI [27].
- More than one course of OTC PPI treatment every 4 months is necessary [33, 34].

Patients on Long-Term PPI: Deprescribing

While therapy for GERD is typically limited to 4–8 weeks, chronic use of PPI therapy is problematic [52]. As the adverse consequences of long-term PPI therapy have become better recognized, deprescribing (i.e., stopping, stepping down, or reducing doses) of PPI therapy in appropriate situations has become an area of focus [53]. An evidence-based guideline targeted at adults over 18 years of age taking a continuous PPI for longer than 28 days for GERD or esophagitis suggests assessing the indication for PPI therapy as the starting point in determining if it is appropriate to deprescribe PPI therapy [52]. Long-term PPI therapy is appropriate for patients with Barrett esophagus, severe esophagitis (grade C or D on endoscopy), documented history of bleeding GI ulcers, and chronic NSAID users with bleeding risk.

An attempt to stop or reduce PPI therapy should be attempted at least once per year in most patients [54]. Questions that will assist in determining if long-term PPI therapy continues to be appropriate or if deprescribing is acceptable are as follows:

- Why are you taking a PPI?
- Have you ever had an upper GI endoscopy before?
- Do you have a history of upper GI bleeding? Ever been hospitalized for GI bleeding?
- Are you currently taking an NSAID (on chronic NSAID therapy)?

Recognize that caution is needed when deprescribing PPI as a recent systematic review of stopping or lowering the dose of PPI in adults compared to long-term daily PPI suggests that on demand prescribing may lead to an increase in GI symptoms [53].

Clinical Pearls

- Assessment of heartburn is aimed at determining if self-treatment is appropriate (including OTC PPI) or whether referral is required. Consider age, comorbid conditions, concomitant medications, presence of alarm symptoms, and other risk factors [4].
- Alarm features and chest pain should be evaluated promptly by a physician to rule out car-

diovascular disease, upper GI carcinoma, and peptic ulcer disease [13, 30].

- Presumptive diagnosis of GERD can be based on clinical symptoms of heartburn and/or regurgitation alone and pharmacists can recommend 2 weeks of OTC PPI therapy for those with frequent heartburn symptoms without further investigation or referral.
- Physician-supervised therapy for GERD is 4–8 weeks long and point-of-care tools are available to assist in shared decision making regarding stopping or reducing doses of PPIs at Deprescribing.org https://deprescribing.org and choosing wisely Canada https://choosingwiselycanada.org/perspectives/how-tos

Links to Major GERD Clinical Practice Guidelines

- American College of Gastroenterology: Guidelines For Diagnosis and Management of Gastroesophageal Reflux Disease (2013) [1]
- World gastroenterology organization global guidelines. GERD global perspective on gastroesophageal reflux disease (2017) [8]
- Canadian Association of Gastroenterology: Canadian Consensus Conference on the management of Gastroesophageal Reflux Disease in Adults, Update (2005) [16]
- Canadian Association of Gastroenterology: Pharmacist-specific Guidelines for the Medical Management of GERD in Adults (2008) [30]

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Fever

10

Mark Diachinsky

Chapter Objectives

1. Describe the etiology, pathophysiology, and categories of fever in different age groups.
2. Conduct initial assessment of patients presenting with fever.
3. Identify red flags in patients presenting with fever that prompt referral to other health-care practitioners or the emergency department.
4. Apply the general principles of antipyretic drug therapy and follow-up assessment or referral in patients with persistent fevers.

Background

A parent comes into your pharmacy requesting something to treat their child's fever. What information do you need to gather to conduct a proper assessment of the child? It is important for pharmacists to have an understanding of the common causes of fevers. In addition, it is important to gather relevant, patient-specific information on symptom assessment and a thorough past medical history in order to make an appropriate recommendation for therapy or referral.

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Definition and Epidemiology

In its simplest definition, fever is any abnormal elevation of core body temperature above the usual range for an individual as a result of the body increasing the temperature set point. Fever, also known as pyrexia, is a complex physiological response that results from the activation of numerous physiological, endocrinologic, and immunologic systems [1]. It is most often associated with infectious sources but can be attributed to non-infectious diseases as well. It is a common reason for patients to seek medical advice, especially in children. In the United States, it accounts for up to 25% of emergency department (ED) visits in children, 15% in the elderly, and 5% in adults [2, 3]. In Canada, it is among the top three reasons for ED visits for patients under 5 years of age [4].

Pathophysiology of Fever

Fever is the result of a biological response mediated and controlled by the central nervous system (CNS), largely in response to circulating cytokines and prostaglandins [5]. The hypothalamus is responsible for regulating body temperature through input from nerve receptors in the skin that measure the surrounding environment relative to the temperature of the blood surrounding the hypothalamus. In response to a trigger, the

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inflammatory cascade releases cytokines, which leads to prostaglandin-2 being released from peripheral tissues, which subsequently raises the hypothalamic temperature set point via cAMP release [3].

Other symptoms often accompany fever due to the physiological response of the body working to maintain the elevated temperature set by the hypothalamus. For example, shivering increases heat production through increased activity of the muscles along with vasoconstriction of peripheral blood vessels to conserve heat [6]. An increase in heart rate may also accompany fevers, anywhere from approximately 3 to 10 beats per minute [7, 8]. Febrile seizures are seizures associated with fevers in childhood without a known cause (i.e., CNS infection or epilepsy). It occurs in 3–5% of children aged 6 months–6 years, and the likelihood of a reoccurrence of a febrile seizure is higher after an initial episode [9]. Febrile seizures can be distressing for children and caregivers, and although antipyretic therapy is commonly initiated to prevent the recurrence of febrile seizures, its efficacy has not been demonstrated, and its use is generally not recommended for these patients [2, 9]. Other symptoms may include somnolence and malaise, cold extremities, hot forehead, and a subjective feeling of cold [6].

Fever is a normal physiological response that aides the immune response. It is usually self-limiting and generally harmless. Presence or absence of fever can be used to monitor the progression of infections. Pharmacological management of fever is mainly for the relief of discomfort associated with fever. Therapy includes the use of antipyretics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Alternating antipyretics is not routinely recommended due to the risk of adverse effects or error in dosing, especially in children. If significant discomfort is present prior to the next dose of an antipyretic, alternating antipyretics should only be considered if proper monitoring of compliance can be ensured. Table 10.1 provides a list of commonly used antipyretics. Various formulations of acetaminophen and ibuprofen are available, and patients should be counseled to read the label to ensure the appropriate dosage. Various cough and cold medicines also contain acetaminophen or ibuprofen, so patients should be advised of the risk of multiple sources of acetaminophen or ibuprofen. Dosages for children are determined based on body weight, and caregivers should be counseled to ensure the correct dosage and formulation are given. In particular, careful attention to liquid concentrations is important, as some medications can come in different concentrations, and

Table 10.1 Commonly used antipyretics

Drug Class	Dose	Adverse reactions
Acetaminophen	*Children:* 10–15 mg/kg/dose Q4-6H PO/PR PRN Maximum 5 doses per day or 75 mg/kg/day (not exceeding adult doses)	Hepatotoxicity (*Note different product concentrations available: 32 mg/mL, 80 mg/mL)
	Adults: 325–650 mg Q4-6H PO/PR PRN Maximum 4 grams per day	
NSAIDs	**Ibuprofen** *Children*: 5–10 mg/kg/dose Q6-8H PO PRN Maximum 4 doses per day or 40 mg/kg/day (not exceeding adult doses) *Adults*: 200–400 mg Q6-8H PO PRN Maximum 3.2 grams per day	GI discomfort, GI bleeding, dizziness, headache, diarrhea, skin rash, allergic reactions, reduced renal function, water retention, platelet dysfunction, Reye's syndrome (ASA in children less than 18 years old) (*Note different product concentrations available: 20 mg/mL, 40 mg/mL)
	Acetylsalicylic Acid (ASA) *Children*: NOT RECOMMENDED *Adults*: 325–650 mg Q4-6H PO PRN Maximum 4 grams per day	
	Naproxen *Children greater than 12 years and adults*: 220 mg Q8-12H PO PRN Maximum 440 mg per day	

GI gastrointestinal, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PR* rectal route, *PRN* when necessary, *Q* every, *H* hours, *PO* oral route

this is a common cause of dosing errors. Nonpharmacological management may include maintaining ambient temperatures, avoidance of physical exertion, removal of excess clothing or bedding, and increasing fluid intake [10].

Hyperthermia

Fever differs from hyperthermia as it results from the body maintaining a higher body temperature through thermoregulatory effectors [5]. In contrast to fever, hyperthermia is an increase in body temperature due to dysfunctional thermoregulation [2]. Hyperthermia is the result of increased heat production or decreased heat dissipation, and therefore a loss of the body's responsiveness to environmental thermal conditions [6]. These heat-related illnesses are often divided into heat exhaustion and heat stroke, or malignant hyperthermia. Heat exhaustion is less severe and results in a core temperature between 37 °C and 40 °C, whereas in a heat stroke, the core temperature exceeds 40 °C [11]. Symptoms of heat exhaustion include anxiety and confusion, dizziness, fatigue, weakness, nausea, headache, hypotension, and cutaneous flushing. Symptoms of heat stroke include anhidrosis, cardiac arrhythmias, hyperventilation, and more severe mental status changes such as, ataxia, coma, irritability, and possible seizures [11]. Management of heat exhaustion includes removal of the person from the hot environment and hydration with continued monitoring. If the condition progresses to heat stroke, the patient requires more immediate cooling, and medical attention must be sought immediately. Hyperthermia can be a life-threatening event and requires immediate attention and first aid.

Diagnostic Criteria

Surprisingly, considering fever is a cardinal symptom reported to clinicians, there has been long-standing controversy of the criteria that defines fever [1]. *Steadman's Medical Dictionary* defines fever as "a bodily temperature above the normal of 98.6°F (37°C)"; however, textbooks in medicine and physiology vary in their definition of the upper limit of normal body temperature from 37.1 °C to 38 °C (98.8 °F–100.4 °F) [1, 12]. The most utilized definition of a fever is a core body temperature of 38 °C (100.4 °F) or higher [2]. A body temperature greater than or equal to 41.5 °C (106.7 °F) is considered hyperpyrexia [3]. However, consideration of the patient is important, as fever is an elevation of core temperature that is normal for an individual and defining a general upper limit of normal for a population may be misrepresentative [1]. It is also important to note that the above definitions refer to core body temperatures, whereas measured temperatures at a particular site (e.g., rectal or axilla) are an estimation of core temperature, and there are substantial differences between sites.

While early investigations by Carl Wunderlich in 1868 demonstrated normal core body temperature of 37 °C, a more recent study showed that core temperatures vary based on age, sex, and time of day [13]. Mackowiak et al. investigated 148 healthy men and women aged 18–40 years and found an overall mean oral temperature of 36.8 °C, with a range of 35.6–38.2 °C. This same study looked at variations during the day and reported a maximum oral temperature (within 99th percentile) of 37.2 °C in the morning and 37.8 °C in the afternoon. The authors concluded that, for young healthy adults, a fever may be more accurately defined as an early morning temperature of greater than or equal to 37.2 °C or a temperature of greater than or equal to 37.8 °C at any time during the day [13]. Additionally, studies have shown that women have higher normal body temperatures than men [13–15]. For women, body temperature varies due to menstrual cycle, with about 0.4 °C higher body temperature during the luteal phase compared to the follicular phase [16]. Elderly populations are generally thought to have lower body temperatures than younger adults; however, comparisons between groups of young and elderly subjects showed that the group of elderly subjects had lower axillary and oral temperatures but had similar rectal temperatures to the young subjects [1, 17]. The normal body temperature in children is not as well defined, although generally tend to be higher than adults

[18]. Overall, infants have higher mean body temperatures that begin to decrease toward adult ranges beginning at approximately 1 year of age, until stabilizing around 13–14 years of age in females and 17–18 years of age in males [1]. Healthy infants can have normal body temperatures as low as 36 °C during sleep and temperatures as high as 37.8 °C during active parts of the day, including after feeding [2]. Due to the considerable variation between individuals and within the same individual, it is not surprising that it is difficult to define an upper limit of normal. While the most common definition of a fever is 38 °C or greater, it is important to consider individual differences, and therefore clinical decisions should be based on the patient's normal temperature variations when available.

Methods of Measurement

Body temperature is most commonly measured in units of Celsius or Fahrenheit, and often the two are used interchangeably. A conversion table between Celsius and Fahrenheit is provided in Table 10.2. The most common methods of measuring body temperature are via the rectum, mouth, axilla, ear, or skin (often forehead, or temporal artery). As previously noted, these measurements provide an estimation of core temperature and vary among sites. While rectal measurements are often considered the gold standard [2, 19–21] because they provide the most accurate estimation of core temperature, this method is also discouraged by other guidelines because of safety concerns, practical issues, and the discomfort it may cause (both physical and psychological) [22, 23]. Additionally, rectal measurements are contraindicated in immunocompromised or neutropenic patients due to the risk of bowel perforation and infection [24]. Oral thermometers are often recommended due to their accuracy; however, they are on average 0.5 °C lower than rectal measurements [2]. This method is not considered suitable for children less than 5 years of age and may be uncomfortable for patients [2]. Axillary temperature measurements are often preferred for their practicality and reasonable accuracy (however, it is also not as sensitive as rectal measurements) [2]. Axillary temperatures may be a more suitable method for infants as they appear to be more reliable and are within 0.25–0.5 °C of rectal temperatures. Axillary temperatures have a greater difference from rectal temperatures in older children (0.5 °C or greater) [2]. Infrared tympanic thermometers are a popular choice among patients, especially parents, due to their ease of use with young children. However, they are not accurate in infants less than 3 months and also have a low sensitivity [2]. Body temperature can also be measured directly from central sites. Central sites include intravascular, urinary bladder catheter, esophageal, and also include the rectum [23]. These are invasive methods, and other than via the rectum, would have to be done under trained health professionals within institutional settings, or an intensive care unit in a hospital. For the ambulatory patient or patients seen in the community, the only feasible central site of measurement is via the rectum. A summary of the recommended sites of measurement for children are shown in Table 10.3. Normal temperature ranges for each site of measurement are depicted in Table 10.4.

Table 10.2 Conversion table from celsius to Fahrenheit for temperature measurements

Celsius (°C)	Fahrenheit (°F)
35.5	95.9
36.0	96.8
36.5	97.7
36.8	98.2
37.0	98.6
37.5	99.5
38.0	100.4
38.5	101.3
39.0	102.2
39.5	103.1
40.0	104
$T_{(°F)} = T_{(°C)} \times 1.8 + 32$	
$T_{(°C)} = (T_{(°F)} - 32)/1.8$	

Etiology

Fever can be caused by infectious and non-infectious causes. Infectious causes are usually due to bacterial or viral infections, but there can

Table 10.3 Recommended sites of temperature measurement

Age	Recommended technique
0–2 years	1. Rectal (most accurate) 2. Axillary Tympanic thermometers not recommended
2–5 years	1. Rectal (most accurate) 2. Axillary or tympanic 3. Hospital setting: temporal artery
> 5 years	1. Oral (most accurate) 2. Axillary or tympanic (or temporal artery if in hospital) 3. Hospital setting: temporal artery

Adapted from the *Canadian Pediatric Society* [21]

Table 10.4 Normal temperature ranges

Method of measurement	Normal range of temperature
Rectal	36.6–38 °C
Tympanic (Ear)	35.8–38 °C
Oral	35.5–37.5 °C
Axillary	36.5–37.5 °C

Adapted from the *Canadian Pediatric Society* [21]

be other causes of infections. Non-infectious causes can include immune-mediated and inflammatory causes, as well as certain drugs, diseases, and malignancies. When the cause of a fever cannot be determined, it is called "fever without source" (FWS) [2]. Height of fever may not define the severity of illnesses; however, there is an association with a greater risk of serious bacterial infections when temperatures are greater than 39 °C, especially in children less than 6 months [2]. Serious bacterial infections can include urinary tract infections, pneumonia, sepsis, or meningitis. Temperatures above 41 °C have been associated with a higher risk of meningitis [2]. Temperature alone does not define serious bacterial infections, and infections can occur in patients with normal temperatures. Physical signs such as pallor, mottled appearance, blue skin color, reduced activity, poor feeding, no smile, decreased response to stimuli, weak high-pitched cry in infants, tachypnea, tachycardia, capillary refill time greater than 3 seconds, and a reduced urine output may be indicative of a serious bacterial infection and should prompt a referral [2]. Symptoms such as vomiting, drowsiness, confusion/irritability, stiff neck/joints and pale blotchy skin may also be signs of sepsis or meningitis. Elderly patients may have less intense fevers in response to infection and may become hypothermic when infected [10, 25]. They have greater morbidity and mortality from infections, and individuals older than 60 years require more careful monitoring [10, 25]. Older individuals are also more susceptible to heatstroke [11]. Table 10.5 outlines possible infectious and non-infectious causes of fever. Non-infectious causes including pulmonary embolism (PE), intracranial hemorrhage (ICH), neuroleptic malignant syndrome (NMS), thyroid storms, heatstroke, and some drug fevers can be more life-threatening [3]. Hyperpyrexia (body temperature greater than 41.5 °C) may occur in sepsis but are more common with those with ICH, neuroleptic malignant syndrome (NMS), and heatstroke [3]. It can also occur with malignant hyperthermia, serotonin syndrome, thyroid storms, anticholinergic toxidrome (e.g., tricyclic antidepressants) or sympa-

Table 10.5 Possible causes of fevers

Infectious causes	Bacterial (e.g., UTIs, otitis media, pneumonia, bacteremia, bacterial meningitis) Viral (e.g., influenza, HIV, viral meningitis) Parasitic (e.g., malaria, toxoplasmosis, giardiasis) Arthropod (e.g., Lyme, Rocky Mountain spotted fever) Fungal (e.g., candidiasis, blastomycosis, histoplasmosis)
Non-infectious causes	Malignancy (e.g., leukemia, lymphoma) Autoimmune (e.g., rheumatoid arthritis, systemic lupus erythematosus) Drug reaction (e.g., allergic reaction, metabolic consequences of a drug, side effect) Vaccinations (more common in children) Environmental fever (e.g., heat stroke, excess exercise) Hyperthyroid or thyroid storm Neurologic (e.g., intracranial hemorrhage) Pulmonary embolus Myocardial infarct Renal infarct Blood transfusion reaction Factitious fever (e.g., Munchausen's vs. Munchausen's by proxy) Neuroleptic malignant syndrome Malignant hyperthermia Serotonin syndrome

Adapted from [3]

thomimetic toxidrome (e.g., amphetamines, cocaine) [3]. Drug fevers are febrile responses related to the administration of a drug [26] and can be caused by various mechanisms. More serious examples of drug fevers include neuroleptic malignant syndrome, serotonin syndrome, or toxic ingestion. The incidence of drug fever is unknown in the general population but occurs in approximately 10% of hospital admitted patients [26]. These fevers may occur at any time during drug therapy but frequently occur after 1–2 weeks of therapy; however, long-term drug therapy should not exclude the possibility of drug fevers [26]. These fevers can sometimes be accompanied by a maculopapular rash. Examples of drugs that can commonly cause fevers and possible known mechanisms can be found in Table 10.6. Furthermore, certain patterns of fevers can also be observed with various diseases (Table 10.7). Patterns may include different rates of temperature changes, fevers during specific times of the day, every 3 or 4 days, in sporadic episodes, or for long periods of time [1].

Symptom Assessment (SCHOLAR)

For proper assessment of a patient's fever, the following information should be collected in order to ensure more urgent follow-up is not required. If the patient is 3 months of age or younger, they should be referred to an urgent care center immediately.

Symptoms

- In addition to fever, did you experience any other symptoms?
- Are you experiencing any nausea or vomiting, diarrhea, runny nose, or cough?
- Are you experiencing any pain?
- Do you have any stiff joints, particularly of the neck?
- Are you feeling more tired than usual, confused, unable to eat or drink?
- For infants, do they have a bulging fontanelle?

Clarifying the symptoms associated with the patient's fever will help identify the presence of any red flags that prompts referral.

Characteristics

- How many days have you had a fever?
- What is the duration of the fever(s), is there a pattern (evening only, morning and evening)?
- How high was the highest temperature measured?

Clarifying the characteristics, height of fever, and patterns of fever will help determine severity of fevers, differential diagnosis of fever vs. hyperthermia, and identifying the presence of any red flags.

History

- Were you doing any exercise or were you out in hot weather prior to/during your fever?
- Have you recently been around any sick contacts?
- Have you recently travelled outside of the country?
- Have you recently received any treatment for cancer or any other immunosuppressant?

Knowing the history of the patient's fever, as well as their relevant medical background, will help determine the severity of the fever and the need to refer the individual to a physician, or seek immediate medical attention.

Onset

- When was your first recorded fever?
- How quickly did your temperature elevate?
- Has your fever abated at all?

Clarifying the immediacy of fever onset and how quickly the fever elevated will help identify the presence of any red flags.

Table 10.6 List of drugs implicated to cause fever

Altered thermoregulatory mechanisms	*Increase body metabolism:* Exogenous thyroid hormones (e.g., levothyroxine), monoamine oxidase inhibitors.
	Vasoconstriction, limiting heat dissipation: Epinephrine, cocaine, amphetamines
	Impair sweating: Anticholinergics (e.g., atropine, antihistamines, tricyclic antidepressants, phenothiazines, butyrophenones)
	Blocking histamine 2 (H2) receptors in the hypothalamus: H2 receptor antagonists (e.g., cimetidine)
	Raising catecholamine synaptic concentrations (sympathomimetic poisoning syndrome): Cocaine, methamphetamines, amphetamines
	Altered function of eccrine sweat glands causing oligohydrosis: Carbonic anhydrase inhibitors (e.g., acetazolamide) Weak carbonic anhydrase inhibitors (e.g., topiramate and zonisamide)
	Altered cytokine levels: Clozapine
Drug administration-related fever	Vancomycin (due to pyrogenic impurities), cephalothin, pentazocine (vaccinations, IM injections), amphotericin B, bleomycin, cytarabine.
Fevers relating to the pharmacologic action	Jarisch-Herxheimer reaction due to release of substances from dying organisms (e.g., treatment of syphilis, borreliosis, leptospirosis, brucellosis, trypanosomiasis). Damage of malignant cells by chemotherapeutic agents
Idiosyncratic reactions	*Malignant hyperthermia caused by a genetic disorder of calcium regulation:* In genetically susceptible patients exposed to inhaled anesthetic agents (halothane, enflurane, isoflurane, methoxyflurane, sevoflurane, cyclopropane, diethyl ether, ethylene), depolarizing muscle relaxants (succinylcholine, decamethonium, gallium), possibly anticholinesterases, ketamine, digoxin, potassium, theophylline, atropine, and glycopyrrolate.
	Neuroleptic malignant syndrome caused by a reduction of dopamine at the synapse of D2 receptors in the CNS: Phenothiazines (fluphenazine, perphenazine, trifluoperazine); butyrophenones (haloperidol, droperidol); thioxanthenes (thiothixene); dibenzapine derivatives (olanzapine, clozapine); tricyclic antidepressants (amoxapine, desipramine, nortriptyline, amitriptyline, clomipramine, imipramine)
	Serotonin syndrome caused by excessive serotonergic activity in the CNS: Selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); serotonin and norepinephrine reuptake inhibitors (desvenlafaxine, duloxetine, venlafaxine); serotonergic drugs (tryptophan, amphetamines, tricyclic antidepressants, trazodone, dextromethorphan, meperidine, fentanyl, tramadol, monoamine oxidase inhibitors, buspirone, lithium, triptans, 5-HT3 receptor antagonists, dihydroergotamine).
	Red cell hemolysis in G6PD deficiency causing release of endogenous pyrogens: Sulfonamides (sulfamethoxazole-trimethoprim, dapsone), antimalarials, nitrofurantoin, quinidine, chloramphenicol, rasburicase.
Hypersensitivity reactions/ Immune-mediated	*Reported drugs (bold indicates most commonly reported drugs):* Allopurinol, aminoglycosides, aminosalicylic acid, amphotericin B, antihistamines, asparaginase, atropine, azathioprine, barbiturates, bleomycin, blood transfusions, carbamazepine, **cephalosporins**, chlorambucil, chloramphenicol, chlorpromazine, cimetidine, clindamycin, colistin, corticosteroids, cytarabine, daunorubicin, diltiazem, folate, haloperidol, heparin infusion, hydralazine, hydroxyurea, imipenem, interferon, iodides, **isoniazid**, IV immune globulin, labetalol, levamisole, macrolides, mebendazole, **methyldopa**, metoclopramide, nifedipine, nitrofurantoin, NSAIDs, novobiocin, pamidronate, **para-aminosalicylic acid**, **penicillins**, **phenytoin**, **procainamide**, procarbazine, propylthiouracil, prostaglandin E2, **quinidine**, ritodrine, rifampin, salicylates, 6-mercaptopurine, streptokinase, **streptomycin**, streptozocin, sulfonamides, tetracyclines, thioridazine, tolmetin, triamterene vancomycin, vitamin preparations

Note: **BOLD** type indicates drug reported more commonly
Adapted from [26]

Table 10.7 Patterns of fevers associated with specific diseases

Pattern	Possible cause
Continuous (sustained) fever, with slight remissions not exceeding 2 °F (16.7 °C)	Lobar and gram-negative pneumonia, rickettsioses, typhoid fever, CNS disorders, tularemia, and falciparum malaria
Intermittent (septic, quotidian, "picket fence") fever with wide fluctuations, usually normal or low in the morning and peaking between 4:00 P.M. and 8:00 P.M.	Localized pyogenic infections and bacterial endocarditis. Malaria may present as quotidian (daily spike), tertian (spike every third day), or quartan (spike every fourth day) Acute brucellosis often as intermittent Salmonelloses, military tuberculosis, double malaria infections, and gonococcal and meningococcal endocarditis often present as double quotidian (two daily spikes).
Saddle-back (biphasic) fever: several days of fever, a distinct reduction in febrile levels for approximately 1 day, and then several additional days of higher fever.	Dengue and yellow fever, Colorado tick fever, relapsing fever, Rift Valley fever, influenza, poliomyelitis, and lymphocytic choriomeningitis
Intermittent hectic (Charcot's) fever: sporadic episodes of fever; periods of normal temperature and recurrence of fever.	Cholangitis (usually associated with cholelithiasis, jaundice, and leukocytosis)
Pel-Ebstein fever, characterized by weekly or longer periods of fever and equally long afebrile periods, with repetition of the cycle.	Hodgkin's disease, brucellosis due to *Brucella melitensis*, and relapsing fever Occasionally in tuberculosis
Reversal of diurnal pattern of fever (typhus inversus), with the highest temperature elevation in the early morning hours rather than during the late afternoon or evening.	Occasionally in military tuberculosis, salmonellosis, hepatic abscess, and bacterial endocarditis
Jarisch-Herxheimer reaction, with sharply increased elevation of temperature and exacerbation of other clinical abnormalities.	Occurs several hours after beginning penicillin treatment for syphilis, in leptospirosis and tick-borne relapsing fever Following tetracycline or chloramphenicol therapy for acute brucellosis

Adapted from [1]

Location

- What was the site of temperature measurement (oral, tympanic, axillary, rectal, etc.)?

Clarifying the location of the temperature measurement will help determine the accurate core temperature and the presence of any red flags.

Aggravating Factors

- What makes the fever worse?
- Does the fever occur after administration of a particular medication?

Fevers are caused by infectious and non-infectious causes. Fevers that are attributable to medications may occur at any time. In hyperthermia, the patient may not be able to tolerate hot environments and will show a progression of hyperthermia symptoms.

Remitting Factors

- What makes it better? Pharmacological and non-pharmacological.
- Were any antipyretics (NSAIDs or acetaminophen) trialed?
- Was the medication effective in alleviating the fever, or symptoms associated?
- How often are you taking medication to alleviate the fever?

NSAIDs and acetaminophen are common antipyretics used to alleviate fever. They are not

effective at alleviating hyperthermia, such as heat exhaustion or heat stroke, as these are conditions associated with an inability of the body to regulate cooling, not due to an elevated core temperature set point by the hypothalamus. Antipyretics may not abate the fever completely but may provide some relief of fever. Information about the duration and dose of antipyretics is important to determine if side effects may occur, such as renal or GI toxicity from NSAID administration, or hepatic toxicity by acetaminophen.

Patient-Specific Characteristics

In addition to assessing the patient's symptoms, a knowledge of the patient's medical and medication history determines the most appropriate plan of management. The following examples illustrate how patient-specific characteristics are essential in fever assessment.

- *Age*: Fever in infants less than 6 months is considered a red flag and prompts referral to a health-care professional for further assessment due to the risk of a serious bacterial infection. Elderly with fevers are also at a greater risk of morbidity and mortality due to infection, and individuals older than 60 years require more careful monitoring and are more likely to require a referral.
- *Pregnancy status*: Pregnant women may require more careful assessment and antipyretic therapy. Studies suggest that fever during the first trimester may be associated with increased risk of neural tube defects and congenital abnormalities [10]. Acetaminophen is the preferred pharmacological therapy, as use of ASA and NSAIDs are associated with side effects, including interference with labor, premature closure of the ductus arteriosus causing pulmonary hypertension in the infant, displacement of bilirubin from protein binding sites in vitro, and inhibition of platelet aggregation in the mother and child if taken close to the time of delivery [10].
- *Past medical history*: Identifying comorbidities may help determine whether an infection is causing fever or if there is a non-infectious cause. Patients who recently had surgery are more at risk of an infection and are more susceptible to fever in general and would require referral [27]. Patients with malignancies or other immunocompromising diseases, such as HIV, are at risk of serious bacterial infection and require prompt referral. Recent travel may be associated with more serious infections and is also a red flag. Some comorbidities may contraindicate the use of specific antipyretics, such as a history of peptic ulcer disease, and therefore, the patient should avoid the use of NSAIDs.
- *Medication history*: Identifying the patient's current medications will help recognize the possibility of drug-induced fever or any possible drug interactions with antipyretic therapy. Many drugs are known to cause drug fever that may occur at any time during drug therapy. It is also important to obtain an accurate medication history to determine the presence of any red flags. For example, patients undergoing treatment with chemotherapy or other immunosuppressive therapies are at risk of serious infections and require prompt referral.

Red Flags

The presence of any of the following red flags prompts referral to a health-care practitioner or the emergency department. These red flags may indicate that the patient has a life-threatening condition.

- *Fever in children less than 6 months*: Children less than 6 months are at greater risk of serious bacterial infections and should be referred to the emergency department for a septic workup. This often includes urine cultures, blood cultures, and a possible lumbar puncture to rule out meningitis.
- *Fever in adults older than 60 years*: Adults greater than 60 years are less likely to have benign causes of fevers and are at greater risk of morbidity and mortality. They require careful monitoring and may require prompt referral to a physician.
- *Fever greater than 40.5 °C*: Patients with fever greater than 40.5 °C are at risk of more serious

infections, including meningitis, and should be referred to a physician for further assessment.

- *Fever for greater than 72 hours*: Fevers lasting longer than 72 hours can indicate a more serious infection and the patient should be referred to a physician for further assessment. Children with fevers lasting more than 5 days should be assessed for Kawasaki's [22]. Additionally, fevers that persist for an additional 24 hours after recommending antipyretic therapy or without any obvious cause should also be referred.
- *Fever associated with a stiff neck*: These symptoms may accompany meningitis. Prompt referral to the emergency department for further assessment, cultures, imaging, and possible lumbar puncture to rule out meningitis is warranted.
- *Fever with seizures*: Febrile seizures occur more commonly in children aged 3 months–5 years [27] and are rarely associated with permanent seizure disorders or neurologic damage. Patients with febrile seizures require assessment by a physician and may require further care/follow-up assessments by a physician.
- *Fever with localized pain, swelling, or heat*: This may be indicative of a thromboembolism, including deep vein thrombosis (DVT) or more serious pulmonary embolism (PE), which should be urgently assessed by a physician, and may require further diagnostic imaging and bloodwork.
- *Fever in patients who have recently travelled*: Recent travelers are at risk of more serious infection, in particular, people who have travelled to developing countries. Incubation times vary and infections can appear shortly after exposure to months following travel. Early evaluation should be completed by a physician, especially in patients that have visited areas with malaria in recent months. Often, the physician will need to alert public health officials if the traveler was contagious while traveling or infected with a pathogen that is a public health concern such as yellow fever or Ebola.
- *Fever in immunosuppressed individuals*: Patients who are immunocompromised are at greater risk of serious infections and require prompt referral to the emergency department for initiation of antibiotics and septic workup. Assessment may include urine and blood cultures, as well as possible diagnostic imaging such as chest X-rays to rule out respiratory infections.
- *Fever in patients who had recent surgery or dental procedure*: Patients are at risk of serious infections or abscesses (which may be difficult to manage with antibiotics alone) after surgical procedures. For example, patients who have undergone recent dental surgery may have infections as severe as endocarditis. These patients should be promptly referred to the emergency department.
- *Fever with lethargy, poor oral intake, difficult to arouse*: These symptoms are often more associated with serious bacterial infections, such as bacteremia or meningitis. Additionally, children that appear very ill, are inconsolable/excessively fussy, or exhibit any symptoms that are worrisome to parents have a higher likelihood of serious infections. Prompt referral to the emergency department is recommended for additional workup and possible imaging.
- *Fever in patients who have recently eaten poorly cooked meat or fish*: Raw foods can put patients at risk of serious infections such as *Salmonella* or *E. coli* O157:H7 (also called the Hamburger Disease). Prompt referral to the emergency department is recommended as these illnesses can cause severe organ damage or death if not treated promptly.

Physical Assessment Skills

Temperature can be measured by a pharmacist when necessary, but a patient can complete this task independently at home with a thermometer. Methods of measurements are shown in Table 10.3.

Additional Assessment Considerations

Since fever can be caused by infections, further investigation to determine the source of the infection is warranted. Rapid antigen testing is avail-

able for community pharmacists to rule out group A streptococci (GAS) throat infection. Urine cultures and blood cultures may be required for moderate to severe infections, or for septic workup. Imaging such as chest X-rays or computed tomography (CT scans) may be completed to diagnose lung infections. If concerned about meningitis, a lumbar puncture may be completed. Laboratory investigations may also be required to determine the risk or presence of infection, as well as response to antimicrobials, particularly by monitoring a complete blood count (CBC) often with a differential to examine the white blood cell (WBC) breakdown.

Clinical Pearls

- Fever is among the most common complaints encountered by health-care professionals and pharmacists are often an early point of contact in the primary care setting.
- Fever is a complex physiological response. There is no definite "set temperature" that defines fever in all individuals. Fever is an elevation of core temperature, which varies among individuals and at different times of the day.
- It is important to know variations of temperatures at different sites of measurement.
- Often fevers are not serious and it is not always necessary to treat a fever with antipyretic therapy. Discomfort from fever can be managed with medications, however patients should be referred to a physician if requiring medications for more than 3 days.
- Acetaminophen and ibuprofen should not be alternated for the treatment of fever.
- Due to the various formulations available, patients should be counseled on reading the label to ensure the correct dosage, especially for children, as different product concentrations may be available. Dosage should be determined based on the child's weight and instructions on the label, with appropriate measuring devices.
- Pharmacists need to complete accurate information gathering in order to identify the need for physician assessment based on red flags and other patient information. The pharmacist's role is to support the relief of discomfort caused by a fever and to rule out more serious infections or hyperthermia, which can lead to significant morbidity and mortality if not promptly managed.

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Dermatological Symptom Assessment

11

Ravina Sanghera and Parbeer Singh Grewal

Chapter Objectives

1. Develop a systematic approach to a dermatological assessment.
2. Identify the key questions that make up a dermatologic history.
3. Utilize appropriate terminology in the description of skin lesions.
4. Describe the morphology of common drug eruptions.
5. Describe initial steps in management of drug eruptions.

Background

The purpose of this chapter is to enable pharmacists to perform a thorough dermatological history and examination, to use a common set of reference terms to describe skin findings, and to recognize some of the most common dermatological conditions pharmacists may encounter. It is estimated that one in six (15%) visits to physicians involves dermatological problems and pharmacists are often the first point of care for many patients seeking a diagnosis and treatment of many common skin conditions [1, 2].

Symptom Assessment

To allow proper assessment of patients presenting with a dermatological presentation, both subjective and objective data must be collected. As a pharmacist, a thorough medical history and physical examination will constitute the dermatological evaluation.

Complete Medical History: History of Presenting Dermatological Issue

Explore the patient's story in relation to their dermatological issue by obtaining relevant information about the presenting illness and any associated or underlying features. Pathology can be divided into two categories, limited exclusively to the skin or a manifestation of a systemic process. Abnormal findings may represent a disease process limited to the skin such as a dermatitis associated with poison ivy exposure or it may refer to a systemic illness such as varicella rash where other organs or body processes may be involved. The line of questioning should glean data that helps identify the manifestation as local

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or systemic, which is paramount for successful diagnosis and treatment.

Symptoms

Common symptoms to inquire about during the history would include pain, burning, stinging, and pruritus. The symptoms should be categorized by when they first manifested, where they are located, if they are intermittent and how severe they are. These symptoms can be described subjectively through questioning the patient (e.g., SCHOLAR) or through patient questionnaires (such as the Dermatology Quality Life Index (DLQI) [3] or through objective assessment instruments if possible (e.g., using the Psoriasis Area Severity Index score (PASI) to grade psoriasis) [4]. Pruritis is a common symptom in most dermatologic conditions such as urticaria and dermatitis. Pain is a less frequently reported symptom and is often secondary to localization of purulent material or nerve inflammation, such as in herpes zoster infection [5]. Additional symptoms may include gastrointestinal disturbances, rheumatological inflammation in bones and joints, neurological changes in sensorimotor function, and/or psychological manifestations like anxiety and depression. To gain a holistic understanding of the impact of the conditions, assessment of other body systems may be appropriate as applicable through a thorough review of systems.

Characteristics

It is important to determine if there have been any appreciable changes over time. Any lesion on the body that has recently grown rapidly, changed color, become asymmetric, or bled or crusted should make you suspect malignant transformation. Cancer would be a less likely concern in a lesion that has remained unchanged for a few or more years; although some patients, especially the elderly, may not be aware of such changes. With generalized rashes, one should ask about where it first arose and how it has progressed over time. A rash such as measles classically begins on the face and then spreads to the trunk and limbs whereas a fixed drug eruption often affects one single area of the skin and does not change location.

Initial changes or lesions should also be elicited as sometimes when patients present to their health-care practitioner their rash has changed and the morphology might differ. For instance, bullae related to impetigo may have been present initially but might have ruptured by the time of examination.

Onset

A key part of history taking is to determine when a lesion or rash first appeared. It may have appeared acutely within recent days or, conversely, may have been present for many years. If the latter, ask why the patient is seeking medical evaluation at this time. A correlation between the onset of the lesions with any particular event or exposure should be explored. In some cases, the patient will have already noted a clear association (e.g., a rash which appeared after the ingestion of a medication). Often, there will be a need to ask several questions to elicit such associations, as patients may be unaware of the importance of various factors. For example, if an allergic contact dermatitis is suspected, the list of possible exposures to consider may be extensive, including cosmetics, detergents, topical medications, and occupational and recreational exposures. Additionally, exposure to sunlight may be an inciting or exacerbating factor; or a recent flu-like illness may lead you to suspect a viral exanthem.

Aggravating/Remitting Factors

It is important from a diagnosis perspective to ask if the patient has received remittance or exacerbation of the condition spontaneously or with any particular therapeutic agents. For example, rosacea may become exacerbated through a host of environmental factors including sun exposure, topical steroid use, alcohol use, caffeine consumption, and other. Improvement with avoidance of these trigger factors and topical or systemic rosacea therapy would help to confirm this diagnosis versus another condition such as lupus erythematosus. Response, or lack thereof, to therapy may also suggest one diagnosis over another. Mistakenly treating a cutaneous tinea infection with topical steroids might lead to mild temporary improvement, however, continued therapy with a steroid will result in subsequent

aggravation and worsening of the condition as the tinea infection will continue to expand.

Complete Medical History: Medical, Medication, Family and Social History

Medical History

When gathering a medical history, obtain a list of chronic medical conditions, recent illnesses, and medical procedures which may suggest a systemic cause of the skin findings. Often skin diseases can be precipitated by a manifestation of an underlying medical condition or a fungal, bacterial, or viral infection. One should also obtain a history of all relevant allergies to both medications and environmental factors.

Medication History

It is essential to make note of current prescription and non-prescription medications, including systemic, injectable, and topical therapy. Gather information on the duration of use, adherence to medications, adverse drug reactions the patient is experiencing, and recently discontinued medications. Some medications are more likely than others to cause dermatologic manifestations, but almost any agent could be implicated. Although newly prescribed medications (taken for days or weeks) are the most likely to cause adverse drug reactions, even those taken continuously for months or years may sometimes cause reactions. Remember that a complete drug history includes the seven "I"s [6]:

- Instilled (eye drops, ear drops)
- Inhaled (nasal and oral)
- Ingested (capsules, tablets, syrup)
- Inserted (suppositories and ovules)
- Injected (IM, SC, IV)
- Incognito (herbs, non-traditional medicine, homeopathic, vitamins, over the counter)
- Intermittent (patients taking medications on an intermittent basis)

Family and Social History

Gather a brief synopsis of the presence or absence of illnesses in the patient's first-degree relatives (i.e., parents, siblings, and children). This may reflect a contagious etiology or common exposure among household members or may suggest the possibility of a hereditary condition such as psoriasis or atopic dermatitis.

Inquiring about a patient's social history, which contains their use of alcohol, tobacco, and illicit drug use as well as nutrition and exercise may be helpful in identifying contributing factors of their dermatological condition and help in the selection of an appropriate therapeutic agent for treatment. In addition, information regarding employment and living conditions may be included and will further contribute to the holistic understanding of the etiology of the patient's dermatologic concern.

Physical Assessment

The extent of the physical exam will depend on the pharmacist's comfort level, nature of practice, and clinical setting. A full dermatological examination would include the skin, hair, nails, and mucous membranes (mouth, eyes, nose, and genitalia). Steps 1 through 4 offer a systematic approach to conducting a dermatologic assessment. The degree of physical examination must be deemed reasonable for the practice setting, purposeful for the treatment of the patient, and supported by the skill set of the pharmacist. An entire body examination is usually unnecessary for a readily identified localized process. However, some findings may be missed if the patient is not examined beyond the most apparent pathology, or that which the patient points out. A medical gown and private examination room should be made available for the patient if the examination goes beyond readily accessible and visible areas. Physical assessment should be performed in a room with sufficient lighting and a penlight can be helpful in evaluating lesions within the mouth or nose. A magnifying glass and ruler may be of assistance in further identifying and quantifying characteristics of the dermatological presentation [6].

Step 1: Physical Examination

Initially, one should assess the overall appearance and disposition of the patient. Essentially, one should see if a patient appears well or if there are signs of a more systemic illness with labored breathing, diaphoresis, sallow skin color, or shortness of breath. If there are any red flags or severe systemic illness, a patient should be instructed to see their family physician or proceed to the emergency room. If the patient is generally well, a full dermatological exam is comprised of an inspection of the skin, hair, and nails. A systematic approach starting from the head and following through to the toes is recommended (Table 11.1). Lesions may be described as outlined in *STEP 2* and if a lesion such as a nevus (mole) is present, make note of any abnormal characteristics, using elements of the acronym *ABCDEs of Melanoma* as warning signs for nevi that warrant further examination (Table 11.2) [7]. Inspect the hair and make note of color, texture, and distribution of the hair. In addition, it may be beneficial to look at the hair shafts which may elude to disorders of increased fragility of hair or parasitic infestations. Lastly, inspect the nail for hypertrophy, subungual hyperkeratosis, abnormal shape or curvature, pitting, and color change. Evaluate the nail bed for separation from the nail plate and hemorrhage. Lastly, nail folds should be inspected for erythema, inflammation, swelling, and tenderness.

Table 11.1 Head-to-toe approach of a dermatological physical examination

Body area	Notes
(a) Scalp and hair	Remove any hair bands or accessories. Make note of alopecia (hair loss) or thinning. Hair morphology of thickness, length, breakage can also be assessed. Assess the scalp for any erythema, scaling, scarring, erosions, or other growths
(b) Head and neck	Includes eyes, nose, and mouth. Flashlight or magnifying glass may be used to assist in visualization. Assess for any lesions or inflammatory rashes. Outer ear and external ear canal as well as behind the ears. In some cases, even inner ear canals can be involved with rashes like psoriasis and discoid lupus. Neck should also be visualized
(c) Torso (back, chest and abdomen)	Remember to inspect the axillae and under the breasts, and in skin folds of obese patients. Once again, note any rashes or lesions
(d) Arms, hands, and fingernails	Inspect sides of fingers and web spaces. Look at dorsum and palms. When examining nails also look at the surrounding area and cuticles (periungual)
(f) Genitalia/ buttocks	Follow site policy. Advised to have another HCP chaperone present. Pubic area and labia in women. Pubic area, scrotum and penis in men
(e) Legs, feet, and toe nails	Evaluate the feet in the same manner as the hands, including interdigital areas and the soles

HCP health-care provider

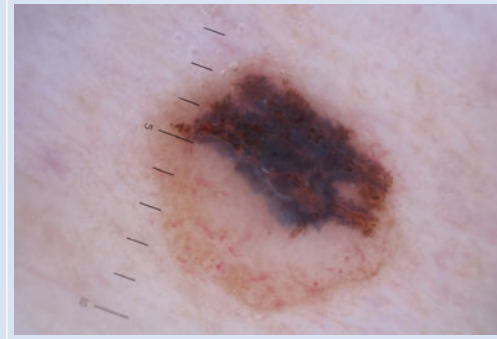
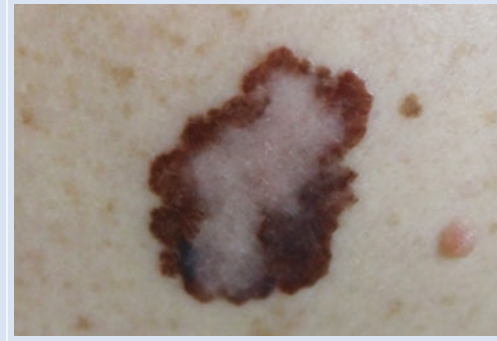
Step 2: Describe and Document Morphology [8]

The word morphology is used by dermatologists to describe the use of descriptors to accurately characterize and document skin lesions. The morphologic characteristics of skin lesions are key elements in establishing the diagnosis and communicating skin findings. Follow the approach outlined in steps (a) through (f) as depicted in Fig. 11.1.

Number and Distribution

There may be one or more lesions in a localized area, or numerous in several areas. The distribution often helps to suggest a plausible etiology. For example, a systemic manifestation of a viral illness like pityriasis rosea will often cause a papulosquamous eruption (both papules and scales present) limited mostly to the trunk, often in a Christmas tree pattern. An eruption confined to one single dermatome (the cutaneous distribution of a single spinal nerve root) is classic for a herpes zoster infection. Lesions on sun-exposed areas, such as the face, dorsal hands, V of the neck and upper chest may suggest a photosensitivity (sun-induced) reaction like polymorphous light eruption.

Table 11.2 ABCDEs of melanoma[a]

Characteristic	Notes	Image
Normal	Symmetric, even border, uniform coloring, smaller than 6 mm, no evolution over months/years	
A. Asymmetry shape	Melanoma lesions are often irregular, or not symmetrical, in shape. Benign moles are usually symmetrical	
B. Border	Typically, non-cancerous moles have smooth, even borders. Melanoma lesions usually have irregular borders that are difficult to define	
C. Color	The presence of more than one color (blue, black, brown, tan, etc.) or the uneven distribution of color can sometimes be a warning sign of melanoma. Benign moles are usually a single shade of brown or tan	
D. Diameter	Melanoma lesions are often greater than 6 mm in diameter (approximately the size of a pencil eraser)	
E. Evolution	The evolution of your mole(s) has become the most important factor to consider when it comes to diagnosing a melanoma. If a mole has gone through recent changes in color and/or size, and/or elevation or if patient experiences any new symptom such as bleeding, itching, or crusting, bring it to the attention of a dermatologist immediately	

[a]Images, used under license from Shutterstock.com

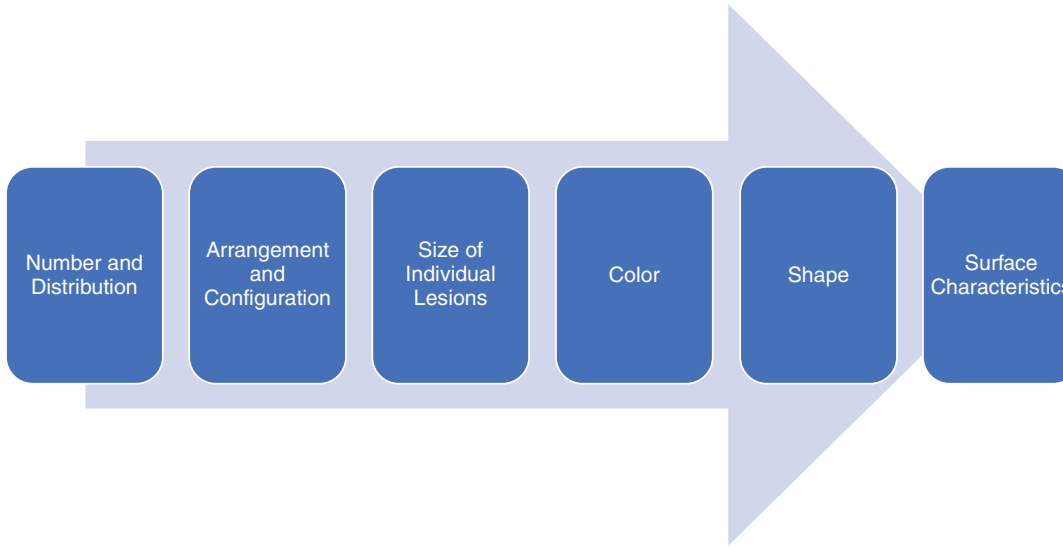


Fig. 11.1 Approach to describing the dermatological lesions

Arrangement and Configuration

Some eruptions can make interesting and characteristic patterns on the skin that can also provide a clue as to their etiology. For instance, an acute dermatitis with well-demarcated linear borders often suggest a contact allergen exposure. Other configurations may be labeled annular (circular) or serpiginous (wavy). Granuloma annulare (an inflammatory dermatosis) and cutaneous tinea infections can both be annular helping us to narrow down our differential diagnosis when these lesions are present.

Size of Individual Lesions

If several lesions are present, they may be similar in size, or there may be a range of sizes. If the latter, you should indicate the range (i.e., 5–15 mm). Nevi on the body are a common example where you will have a tremendous range of sizes of lesions.

Color of Lesion

Skin lesions may present in a multitude of colors and uniformity. Hypopigmented skin is an area which is lighter in color than the surrounding skin and hyperpigmented areas are darker in color than the surrounding skin. Noting uniformity (or non-uniformity) of color is important. A lesion may have an erythematous ring around the periphery with a flesh-colored center. Another lesion may be a uniform light brown or it may be unevenly colored shades of brown; both could be rightly labeled hyperpigmented, but a more precise description is necessary to distinguish the two. For example, when a patient has completely white or depigmented areas of skin the most common diagnosis is vitiligo.

Shape and Lesion Morphology

Lesions on the skin are categorized in terms of the primary morphology and secondary features. Primary lesions are initial lesions that have not been altered by trauma or manipulation and have not regressed. The most common primary morphological terms include: Macules, patches, papules, and plaques. Secondary lesions develop during the evolutionary process of skin disease or are created by manipulation or complication of primary lesion (e.g., rubbing, scratching, scaling, and infection). Table 11.3 describes the various types of primary and secondary lesions and common differential diagnoses based on morphology.

Surface Characteristics

On occasion, primary and secondary morphological terms might not give enough information

to render an accurate diagnosis. Other terms can be used to describe the surface morphology of a lesion or rash. Terms such as smooth, rough, shiny, dull, waxy, verrucous (warty), keratotic (thickened skin), filiform (finger or thread like) can all be applied. For example, the surface of a wart can be described as being rough, verrucous, keratotic, and/or filiform. A mole on the other hand would normally be described as smooth or domed.

Table 11.3 Description of primary and secondary lesions and common differential diagnoses[a]

Term	Description	Image	Example
Primary lesions			
Macule	Flat lesion, less than 1 cm		Freckle (small, pigmented lesions on sun-exposed areas) Viral exanthem (erythematous rashes arising focally and spreading) Idiopathic guttate hypomelanosis (small depigmented white spots on sun-exposed areas)
Patch	Flat lesion, greater than 1 cm		Vitiligo (depigmented areas of skin and hair) Viral exanthems (erythematous rashes, most often have fever or systemic symptoms) Alopecia areata (smooth, bald patches in hair-bearing areas)
Papule	Raised lesion, less than 1 cm		Wart (domed or filiform papules with thrombosed capillaries and surrounding callus) Insect bite/sting (discrete, painful, or itchy lesion) Basal cell carcinoma (telangiectatic, pearly, domed nodule)

(continued)

Table 11.3 (continued)

Term	Description	Image	Example
Plaque	Raised lesion, greater than 1 cm		Psoriasis (scaling, erythematous rash usually seen on extensor surfaces) Atopic dermatitis (itchy, thickened skin, and accentuated skin markings usually in flexural areas) Granuloma annulare (raised, annular rash on dorsal hands or feet) Tinea cruris (raised, annular rash with scaling borders)
Vesicle	Fluid-filled lesion, less than 1 cm		Herpes simplex virus (discrete, clustered, painful blisters) Dyshidrotic eczema (small blisters on the sides of fingers and toes, very itchy) Varicella zoster virus (widespread blisters in chicken pox and dermatomal blisters in shingles, usually painful)
Bullae	Fluid-filled lesion, greater than 1 cm		Bullous pemphigoid (autoimmune blistering disease) Bullous impetigo (large, flaccid blisters often seen in children) Edema blisters (seen in the legs of patients with severe stasis dermatitis and lower limb edema)
Nodule	Elevated, solid lesion, greater than 1 cm, usually in the dermis or subcutaneous lesion		Dermatofibroma (firm, skin colored to red to brown nodule in the dermis, usually after trauma) Acne (firm, painful lumps under the surface of the skin, unable to express discharge or fluid) Lipoma (soft, subcutaneous, rubbery swellings)

Table 11.3 (continued)

Term	Description	Image	Example
Cyst	A papule or nodule that contains fluid or semi-solid contents		Epidermoid inclusion cyst (subcutaneous, mobile lesion filled with keratin) Acne (subcutaneous nodules, often not as mobile, filled with pus)
Pustule	A discrete lesion that contains purulent material or neutrophils		Acne (small lesions on the surface where pus can be expressed) Pustular psoriasis (can develop pustules, mainly on palms and soles) Folliculitis (pustules located discretely at sites of hair follicle openings)
Wheal	Raised erythematous lesions with surrounding hypopigmentation		Chronic spontaneous urticaria (idiopathic eruption of wheals and possibly angioedema, with itch) Bites and stings (usually discrete, itchy areas following exposures) Drug eruption (widespread, itchy, inciting drug usually started within several days or weeks of outbreak)
Secondary lesions			
Scale	Desquamated skin cells that peel and flake off		Seborrheic dermatitis (greasy yellow flaking in glabella and nasolabial folds) Tinea infections (annular plaques with peripheral scale and central clearing)

(continued)

Table 11.3 (continued)

Term	Description	Image	Example
Licheni-fication	Thickened areas of skin with enhanced skin markings		Lichen simplex chronicus (chronically excoriated papules and plaques of skin)
Crust	Plasma that has exuded and solidified into scale		Impetigo (honey-colored crusting on an erythematous base)
Erosion	Superficial loss of surface epithelium		Herpes simplex virus (eroded and/or crusted solitary or clustered lesions on mucosal surfaces like the lip)

Table 11.3 (continued)

Term	Description	Image	Example
Ulceration	Deeper loss of both surface epithelium and dermis		Venous leg ulcer (open wounds on a background of edematous skin with varicosities and possibly hemosiderin deposition)
Atrophy	Loss of epidermis, dermis, or subcutaneous tissue		Lichen sclerosus (pink to erythematous thinning of skin with white scarred and/or atrophic areas)
Hypertrophy	Thickening of epidermis, dermis, or subcutaneous tissue		Keloid scar (pink to skin colored to hyperpigmented papules and plaques, usually on upper torso and ears)

[a]Images, used under license from Shutterstock.com

Step 3: Palpate the Lesion [1]

When applicable, palpate the lesion. Palpation should always be conducted while wearing gloves. Never palpate an inflamed area, because this may cause a possible infection to spread deeper and produce intense pain. When palpating, carefully run your index finger over the lesion and note the texture of the surface (i.e., rough or smooth). At times you may be able to distinguish a slightly raised lesion from a flat one by careful palpation with the eyes closed. Next, determine the consistency by pressing on the lesion and then palpating it between your fingers. Terms used to describe consistency include rock-hard, firm, rubbery, fluctuant, and soft. Also, note how far the lesion extends below the skin surface by feel and if it is fixed in place or freely mobile.

Laboratory and Diagnostic Tests

In most cases, a good history and physical examination can often help the practitioner to arrive

at a diagnosis and management plan. However, in some cases further diagnostic testing may be required. If a diagnosis is unclear, the patient might have to see their physician or dermatologist for a skin biopsy. The skin biopsy is one of the most valuable diagnostic tools available and can greatly aid in arriving at a timely and correct diagnosis. Other diagnostic tests include swabbing skin lesions or taking skin scrapings to rule out bacterial, viral, and fungal infections. Bloodwork can also be of great utility in diagnosing skin conditions associated with systemic features or underlying internal medical conditions. In some cases, patients are also sent for skin prick allergy testing and/or patch testing when allergies are believed to be involved in their presentation.

Pharmacist's Role in the Monitoring and Therapy of Dermatological Diseases

Pharmacists and other health-care providers may encounter numerous challenges in the treatment of dermatological diseases. Patient surveys have found treatment non-adherence rates as high as 73% in certain dermatological diseases such as in the psoriasis population, which can create a vicious cycle between disease exacerbation and treatment failure leading to poor patient outcomes [9]. The most commonly cited reasons for patient non-adherence include frustration with medication efficacy, inconvenience of administration, and fear of adverse effects [9]. Poor adherence is both a cause and consequence of inadequate treatment efficacy as the patient perceives it. When developing a treatment plan, it is paramount to engage the patient in treatment decisions and understanding any reasons why the patient might or might not adhere to any specific therapy.

Pharmacists are in an ideal position to enhance adherence to therapy. Factors that are associated with better adherence include choosing the simplest therapy and dosing regimen that suits the patient's lifestyle, providing easy-to-understand instructions for medication use, and appropriately conveying information about therapy risk. It has also been shown that a collaborative model of management that consists of regular follow-up visits and good health-care practitioner-patient relationships further improves adherence [10].

Managing patient expectations and conveying the chronic nature of particular dermatological diseases (e.g., acne, rosacea, and psoriasis) is instrumental in enhancing the patient's commitment to therapy. Key goals of dermatological disease therapy are generally to clear skin lesions, mitigate systemic and local symptoms, and improve quality of life. However, treatment satisfaction is an important factor that may be overlooked. Treatment satisfaction encompasses efficacy and safety as well as convenience of therapeutic regimen, ease of administration, and cost or coverage of medication/therapy. In some instances, treatments may take several days or up to several weeks to see maximal benefit. Inadequate efficacy or loss of efficacy should be evaluated thoroughly by addressing the patient's adherence to the regimen before making or suggesting a change in treatment approach. Importantly, patients should be encouraged not to abruptly discontinue their medication unless directed by a health-care provider as this can also trigger a relapse in disease control. Adherence to medications should be assessed at routine refills as well as a periodic review of the medication profile to identify any medications that have a potential to exacerbate the dermatological condition. Regular follow-ups are not only beneficial in enhancing adherence but also allows for early detection and intervention to manage the comorbidities associated with various dermatological conditions (e.g., psoriatic arthritis with psoriasis, depression associated with chronic urticaria) [11]. Addressing all these facets of therapy are vital to designing a treatment plan that will complement the patient's routine and treatment the patient would be willing to use.

When pertinent, reinforcement of healthy lifestyle behaviors and providing solutions to avoid established triggers as applicable should all be part of a comprehensive treatment plan. Adjustments in therapy should be considered depending on patient response (efficacy and adverse effects). Referrals to a specialist should be considered when disease is extensive, distressing, and unresponsive to current therapy or if the patient is experiencing unmanageable adverse reactions to topical or systemic therapy. Table 11.4 provides a

Table 11.4 Adverse effects and monitoring parameters for commonly prescribed dermatological agents [15–17]

Drug	Examples[a]	Possible adverse effects and suggested monitoring parameters[a, b]	Additional notes (Clinical pearls)[a, b]
Topical			
Corticosteroids	*Low potency*: Hydrocortisone *Medium to high potency*: Beclomethasone Betamethasone Mometasone *Ultra-high potency*: Clobetasol	Application site: Irritation (due to vehicle most often) Pruritus/burning Folliculitis Contact dermatitis Hypertrichosis Acneiform eruptions Pigmentation change Miliaria Atrophy Striae Telangiectasia; purpura; impaired wound healing; steroid rosacea	Caution in active viral, fungal, parasitic infections, infections that may be exacerbated by immunosuppression (e.g., HSV, VZV). Caution with periocular use with history of cataracts and/or glaucoma Systemic corticosteroid side effects (Cushing's syndrome, adrenal crisis) with use of vast topical quantities
Retinoids	Tretinoin Tazarotene Adapalene	Application site: Erythema/peeling Burning/stinging Pruritus/dryness Tenderness/pain Contact dermatitis Increased photosensitivity (less with adapalene); skin fissure/cheilitis	Tazarotene contraindicated in pregnancy Topical retinoids not used in pregnancy
Topical antibiotics	*Macrolides*: Erythromycin Clindamycin	Application site: Dryness Contact dermatitis	Enhanced efficacy when used in conjunction with benzoyl peroxide
Other Antibacterials	Benzoyl peroxide	Application site: Contact dermatitis Stinging/erythema Burning/pruritus Dryness/peeling Increased risk of photosensitivity reactions; bleaching of hair and clothing; lingering odor	Caution if sensitivity to balsam of Peru or cinnamon

(continued)

Table 11.4 (continued)

Drug	Examples[a]	Possible adverse effects and suggested monitoring parameters[a, b]	Additional notes (Clinical pearls)[a, b]
Calcineurin inhibitors	Tacrolimus Pimecrolimus	Application site: Burning/stinging Soreness Pruritus Tingling Erythema Flu-like symptoms; acne/folliculitis development due to occlusive formulation	Warning: Rare cases of skin malignancy and lymphoma have been reported in patients treated with topical calcineurin inhibitors. Avoid continuous long-term use. Controversial as human studies have shown no further risk Do not use in immunocompromised patients and active infection
Exfoliants/ Comedolytic agents	Salicylic acid	Application site: Irritation Burning Erythema Peeling Increased risk of photosensitivity reactions	
Other	Dapsone	Application site: Peeling Dryness Erythema Burning Irritation	Can be combined with adapalene and benzoyl peroxide
Systemic			
Retinoids	Isotretinoin Acitretin	Hyperlipidemia; depression; increased photosensitivity; dermatitis; alopecia; dry eye/blurred vision; reduced visual acuity; dry mucosa/lips; epistaxis/ cheilitis; oropharyngeal pain; URTI; arthralgia/myalgia; auditory impairment; inflammatory bowel disease Lab tests to monitor: Liver tests (AST, ALT, ALP) Lipids (TG, LDL, cholesterol) Blood glucose Thyroid (TSH) CBC (Complete Blood Count) with diff Pregnancy testing (hCG)	Pregnancy risk factor X (do not use in pregnancy or breast feeding). Must abstain from pregnancy for 3 years after use of acitretin Do not use if sensitivity to other retinoids, Vitamin A, or its metabolites Monitor consumption of other sources of Vitamin A (risk of hypervitaminosis A) Avoid use with alcohol. For acitretin, female patients should abstain from ethanol or ethanol-containing products during therapy and for 2 months after discontinuation Caution in patients with predisposition or history of bone loss Do not use concurrently with tetracyclines due to risk of pseudotumor cerebri May cause depression, mood disturbances, and suicidal ideation. Discontinue use and refer for further assessment

Antibiotics	*Tetracyclines*: Tetracycline Doxycycline Minocycline	Fatigue/drowsiness Headache/dizziness Vertigo/ataxia Increased photosensitivity Acne N/V/D/anorexia Hyperpigmentation (minocycline) Esophagitis/esophageal ulcer	Not to be used in pregnancy/lactation, in children <8 yo (unless these are the only effective or safest option) Autoimmune syndromes: Lupus-like, hepatitis, and vasculitis autoimmune syndromes (including serum sickness, e.g., fever, arthralgia, and malaise) have been reported; discontinue if symptoms occur and assess liver function tests May be associated with increases in BUN (Blood Urea Nitrogen). Use caution in patients with renal impairment as this may lead to azotemia, hyperphosphatemia, acidosis, and possibly to drug accumulation and potential hepatotoxicity Risk of myasthenia gravis Risk of pseudotumor cerebri (concurrent use with systemic retinoids)
	Macrolides: Erythromycin Clarithromycin Azithromycin	Rash Tinnitus, hearing loss GI effects include abdominal pain and cramping, N/V/D, jaundice, hepatitis Arrhythmia Seizure Weakness Super infection (C. difficile, candida)	Caution in patients with liver dysfunction, history of cholestatic jaundice, or hepatic dysfunction with prior azithromycin use Concurrent use with CYP3A4 inhibitors

(continued)

Table 11.4 (continued)

Drug	Examples[a]	Possible adverse effects and suggested monitoring parameters[a, b]	Additional notes (Clinical pearls)[a, b]
Immuno-suppressants	Methotrexate (MTX)	Bone marrow suppression; malaise/fatigue; chills/fever Neurotoxicity; drowsiness/dizziness GI (nausea, vomiting, diarrhea); shortness of breath; headaches; rashes, oral ulcerations; hepatotoxicity; pneumonitis; nephritis Labs: Liver tests (AST, ALT, ALP) Albumin SCr/urea CBC diff Pregnancy (hCG)	Do not use in pregnancy/lactation Folic acid should be given on days before/after MTX. Supplementation of MTX with folic acid improves tolerability
	Cyclosporine	Hyperlipidemia; neurotoxic; tremor/headache; gum hyperplasia URTI; hypertension (monitor blood pressure); GI effects N/V/D/abdominal pain Nephrotoxic; hyperkalemia; hyperuricemia; myalgia; malignancy (skin cancer especially); bone marrow suppression Labs: Potassium/magnesium LFT/bilirubin Lipids SCr (fasting)/urea Urinalysis CBC diff	Do not use in pregnancy/lactation (females of childbearing potential), immunodeficiency syndromes, alcoholism (not absolute), liver disease, renal impairment Monitor for blood dyscrasias Drug interactions (see product monograph)
Other	*Apremilast*	Headache URTI Weight loss GI effects N/V/D Depressed mood Tachyarrhythmia Labs: SCr (not routine use, only with those with kidney failure)	Do not use in uncontrolled infection, immunodeficiency (except autoimmune disease), malignancy (except non-melanoma skin cancer), uncontrolled HTN, reduced renal function, pregnancy, and lactation.

Biologics	*TNFi (Tumor Necrosis Factor Inhibitor) inhibitors* Adalimumab Etanercept Infliximab	Injection site reactions Infusion reaction (infliximab only) Risk of infections (URTI, LRTI, skin, other) TB reactivation Oral herpes Oropharyngeal pain Arthralgia Headache/fatigue Skin rashes Lupus-like syndrome Bone marrow suppression *Labs (pre-screening)*: CBC with diff Chest X-ray TB test HBV, HCV, HIV Antinuclear antibody (ANA)	Do not use or suspend treatment in severe active infection (sepsis, active TB, opportunistic infections, hepatitis) Contraindicated in demyelination disease. Monitor for neurological disease Contraindicated in heart failure (NYHA (New York Heart Association) class III/IV) Caution and monitor in patients with history of previous lymphoma or malignancy. Caution in pregnancy and lactation. Review patient's vaccination history prior to initiating therapy
	IL-17A inhibitors: Ixekizumab Secukinumab Brodalumab	Injection site reactions Development of infection (increased rates of staph and candida infections) Neutropenia; fatigue; nausea/diarrhea; Arthralgia/myalgia Exacerbation of inflammatory bowel disease *Labs (pre-screening)*: CBC with diff Chest X-ray TB test HBV, HCV, HIV ANA	Do not use or suspend in active infections (see TNFi inhibitors) Active inflammatory bowel disease (brodalumab is contraindicated) Brodalumab and risk of suicidal ideation (black box warning; see product monograph) Caution and monitor in patients with history of previous lymphoma or malignancy. Caution in pregnancy and lactation Review patient's vaccination history prior to initiating therapy
	IL12/23 inhibitors Ustekinumab *IL 23 inhibitors* Guselkumab	Injection site reactions Increased incidence of infections; headache; nausea/diarrhea; arthralgia Neurotoxicity (rare); pneumonitis (rare); malignancy (unclear risk) *Labs (pre-screening)*: CBC with diff Chest X-ray TB test HBV, HCV, HIV ANA	Do not use or suspend in active infections (see TNFi inhibitors) Caution and monitor in patients with history of previous lymphoma or malignancy. Caution in pregnancy and lactation Review patient's vaccination history prior to initiating therapy

ANA antinuclear antibody, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *D* diarrhea, *GI* gastrointestinal, *hCG* human chorionic gonadotropin, *HSV* Herpes simplex virus, *HTN* hypertension, *LRTI* lower respiratory tract infection, *N* nausea, *SCr* serum creatinine, *TSH* thyroid stimulating hormone, *URTI* upper respiratory tract infection, *VZV* varicella zoster virus

[a]List not all-inclusive

[b]If known hypersensitivity to the active ingredient or any other components of the formulation, use is contraindicated

summary of common adverse effects and parameters for monitoring of commonly prescribed medications in dermatology.

Drug Reactions

The purpose of this section is to help pharmacists develop a clinical approach to the evaluation and initial management of patients presenting with drug reactions. It is always astute to consider drugs as the cause of a skin eruption. Most cutaneous drug reactions are inflammatory, generalized, and symmetrical. Diagnosis is established by clinical features including morphology and timing.

The most common types of drug reactions include exanthematous or morbilliform eruptions, urticaria, fixed drug eruptions, drug-induced hypersensitivity syndrome (DIHS), also called drug reaction with eosinophilia and systemic symptoms (DRESS) and epidermal necrolysis which includes Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Some individuals may be at a higher risk for the development of drug reactions than others (Table 11.5).

Table 11.5 Patient risk factors for drug reactions [12]

Risk factors for drug reactions	Notes
Female	
Prior history of drug reaction	
Recurrent drug exposure	Repeated courses of therapy with the same drugs or related drugs are associated with higher rates of adverse drug reactions
HLA type	HLA-B*1502: carbamazepine and SJS/TEN in Han Chinese, SE Asians HLA-B*5701: abacavir and DRESS in whites, Hispanics HLA-B*5801: allopurinol and SJS/TEN in Han Chinese, Taiwanese, Thai
Certain disease states	Reactions to aminopenicillins occur more commonly in patients with Epstein Barr virus (EBV) infection. HIV-positive patients have high rates of dermatologic reactions to sulfonamides and other drugs

Risk factors include female sex, prior history of drug eruptions, recurrent drug exposure, and different genetic HLA types. Drug-induced skin reactions can be classified according to timing into immediate reactions and delayed reactions. Immediate reactions occur less than 1 hour after the last administered dose, such as flushing from niacinamide. Delayed reactions generally occur after 1 hour, but usually more than 6 hours and occasionally weeks to months after the start of administration [6].

The role of allergy testing is of limited value in evaluating adverse cutaneous reactions to medications as most drug-related reactions cannot be reproduced through percutaneous testing. Penicillin is the exception to this rule. Penicillin skin testing is the preferred method of evaluation of possible type I, IgE-mediated penicillin allergy (urticaria due to penicillin) [6, 12].

Drug Timelines [6]

The most important information in determining if a rash is medication-related is its timing. When starting a timeline, start with the onset of the rash as Day 0, and work backward and forward creating a drug timeline that encompasses all the medications, herbals, supplements, and over-the-counter products the patient has been taking (Fig. 11.2). The inciting culprit drug is usually one that has been initiated prior to Day 0 and overlaps Day 0 and possibly beyond.

Exanthematous Drug Eruptions

Exanthematous eruptions are the most common of all cutaneous drug eruptions (~90%) and manifestation is generally limited to the skin. The lesions present as widespread erythematous macules which initially appear on the trunk and spread centrifugally to the extremities in a symmetric fashion. The patient may indicate pruritus and a fever may be present. Skin lesions usually appear more than 2 days after the drug has been started, mainly around days 8–11, and occasionally persists several days after having stopped the drug [6].

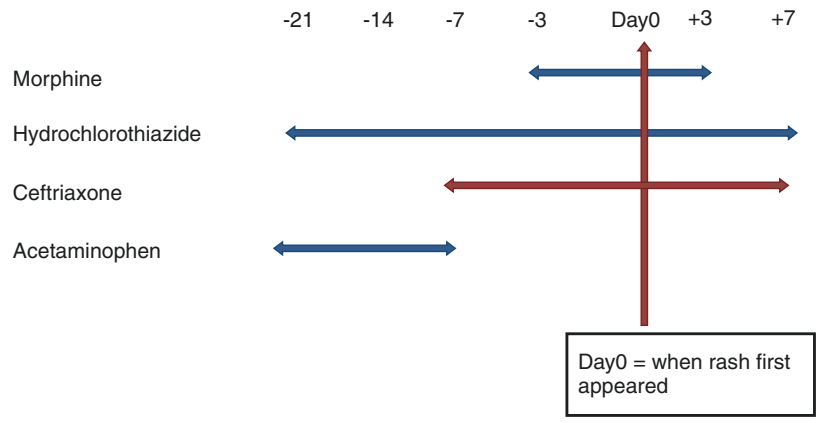


Fig. 11.2 Example of drug timeline

The clinical course of the eruption usually resolves in a few days to a week after the medication has been discontinued. In some cases, the medication may be continued by the care provider if the eruption is not too severe and the medication cannot be substituted. The eruption generally resolves without sequelae though extensive scaling and desquamation may occur. Management of exanthematous eruptions usually consists of a course of topical steroids, with the addition of oral antihistamines if warranted.

Table 11.6 Drugs commonly implicated in urticaria, angioedema, and anaphylaxis[a]

Drug	
Antibiotics Penicillins, cephalosporins, sulfonamides	Anti-hypertensives Angiotensin-converting enzyme inhibitors, calcium channel blockers
Histamine-releasing drugs Opiates, amphetamines, aspirin	Oral contraceptives

[a]Not an inclusive list

Urticarial Eruptions [13]

Urticaria refers to the development of wheals on the skin and angioedema refers to the development of deeper subcutaneous swelling in the skin. Acute urticaria is defined as lasting less than 6 weeks and chronic lasting greater than 6 weeks. Clinically, this manifests as itchy, erythematous, edematous papules, and plaques, often surrounded by a vasoconstricted halo. Individual lesions often last less than 24 hours and are characterized by spontaneous appearance and resolution in completely random areas on the skin and/or subcutaneous tissues. Anaphylaxis is a severe form of these reactions often characterized by swelling in the throat, difficulty breathing, hypotension, and possibly even death if medical treatment is not provided. These reactions can occur immediately after the administration of a food or medication, or can sometimes be delayed as well. Table 11.6 depicts drugs commonly implicated in Urticaria, Angioedema, and Anaphylaxis.

Management includes identifying and trying to eliminate any potential offending agent, and avoiding re-exposure or re-challenge in the future. First-line medical management includes the use of second-generation, non-sedating H1 antihistamines at regular or supra-therapeutic doses. In cases of chronic urticaria, where first-line treatments fail after maximal titration, patients can be initiated on the biologic omalizumab. In cases of anaphylaxis, patients should be given an epinephrine injection (e.g., EpiPpen®) to inject and proceed immediately to the hospital.

Fixed Drug Eruption [6, 14]

A fixed drug eruption is an adverse drug reaction characterized by the formation of an erythematous patch or plaque that will recur at the same site with

Table 11.7 Drugs commonly implicated in fixed drug eruptions[a]

Drug	
Phenolphthalein (laxatives)	Barbiturates
Tetracyclines	NSAIDS
Metronidazole	Salicylates
Sulfonamides	Food dyes (yellow)

NSAIDS nonsteroidal anti-inflammatory drugs
[a]Not an inclusive list

re-exposure to the drug. This distinguishing feature is why this eruption is classified as "fixed." Early lesions are sharply demarcated erythematous macules and become edematous, forming a plaque, which may evolve to become a bulla (blister) and then an erosion. The lesions are commonly solitary, however, they may be multiple with random distribution. In previously sensitized individuals, lesions may occur from 30 minutes to 8 hours after ingesting the drug. A list of commonly implicated drugs are listed in Table 11.7.

The clinical course of the eruption usually resolves days to weeks after the drug is discontinued. Non-eroded lesions can be treated with a potent topical corticosteroid ointment. Eroded cutaneous lesions can be treated with a protective or antimicrobial ointment and dressing until the site has re-epithelized. Patients may experience pain with the eruptions, especially for lesions on mucosal regions. In these cases, pain management should be addressed.

Drug-Induced Hypersensitivity Syndrome [6, 12]

Drug-induced hypersensitivity syndrome (DIHS) is also known as drug reaction with eosinophilia and systemic symptom (DRESS). A skin eruption is accompanied by systemic symptoms and internal organ involvement (e.g., liver, kidney, heart, and bone marrow). The eruption typically presents as an exanthem, erythematous centrofacial swelling with fever, malaise, and lymphadenopathy. Over 70% of patients will present with eosinophilia as well. In addition, liver function test abnormalities and/or hepatosplenomegaly are

Table 11.8 Drugs commonly implicated in DIHS/DRESS[a]

Drugs	
Allopurinol	Anticonvulsants Phenytoin Carbamazepine Lamotrigine
Antibiotics Sulfonamides Penicillin Minocycline Metronidazole	NSAIDS Sulindac Diclofenac Meloxicam
Anti-TB drugs Isoniazid	Anti-HIV drugs Abacavir

DIHS drug-induced hypersensitivity syndrome, *DRESS* drug reaction with eosinophilia and systemic symptoms, *NSAIDS* nonsteroidal anti-inflammatory drugs
[a]Not an inclusive list

helpful diagnostic tools. More specifically, the clinician should order CBC, LFTs (Liver Function Tests), BUN, and creatinine as the liver, kidney, and bone marrow are common targets. Signs and symptoms of (DIHS/DRESS) typically begin in the third week after the start of the medication or after increasing a medication dose, however, the range may be as little as 1 week and up 12 weeks. Fatality rate of DIHS/DRESS may be up to 10%. See Table 11.8 for commonly implicated drugs.

Signs and symptoms of DIHS/DRESS may persist and recur for many weeks after the cessation of drug treatment. It is paramount that all suspect medications are stopped or substituted and all non-essential medications are discontinued. Therapy may consist of the use of topical steroids, systemic antihistamines, and, in severe cases, systemic steroids may be initiated to avoid impending organ failure. There is a need to continue monitor organs for functional decline.

Epidermal Necrolysis Spectrum [6, 12]

The epidermal necrolysis spectrum consists of both Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) which are both acute life-threatening mucocutaneous reactions and constitute a dermatologic emergency. Patients

Table 11.9 Drugs commonly implicated in toxic epidermal necrolysis[a]

Drug	
Sulfa antibiotics, sulfasalazine	NSAIDs
Allopurinol	Nevirapine
Tetracycline	Thiacetazone
Anticonvulsants (carbamazepine, lamotrigine, phenobarbital, phenytoin)	

NSAIDS nonsteroidal anti-inflammatory drugs
[a]Not an inclusive list

are classified into one of three groups according to body surface area (BSA) involvement (SJS <10%, SJS/TEN 10–30%, TEN >30%). Mortality rates vary from 5% to 12% for SJS and greater than 20% for TEN [6]. Increasing age, significant comorbid conditions, and greater extent of skin involvement correlate with poorer prognosis. Over 100 different drugs have been associated with SJS/TEN, and the highest risk agents are listed in Table 11.9.

These two conditions represent similar processes but differ in severity based on the body surface area that is involved. They are characterized by extensive necrosis and detachment of the epidermis and mucosal surfaces. Clinical presentation typically begins within 8 weeks after the onset of drug exposure. Mucous membrane involvement (buccal, ocular, genital), fever, headache, rhinitis, and myalgias may precede the lesions by 1–3 days. Eruption is initially symmetric and distributed on the face, upper trunk, and proximal extremities. Early skin lesions are characterized by erythematous, irregularly shaped, dusky red to purpuric macules which coalesce as they progress. Lesions evolve to flaccid blisters and the necrotic epidermis is easily detached at pressure points or by frictional trauma, revealing large areas of exposed, red, sometimes oozing dermis.

Early recognition and the withdrawal of the offending drug(s) is paramount to prognosis. In case of doubt, all non-life-sustaining drugs should be discontinued. Care should proceed in a burn unit for patients with >25–30% BSA involvement and extensive supportive care is needed.

Clinical Pearls

- Always take a comprehensive history and perform a physical examination if possible when a patient presents with a rash or lesion in order to determine if this is an issue that can be dealt with at the pharmacy level or should be referred to a physician
- Use correct, precise, and common terminology when describing rashes and lesion to ensure accurate records and to be able to communicate with other health-care practitioners using a common language
- If patients present with a rash, along with systemic symptoms such as fever, facial edema, or malaise, refer to a physician for prompt assessment
- Never forget the 7 "I"s when looking for causative agents of drug reactions
- When creating a drug timeline, always use Day 0 as your starting point and work forward and backward to determine the culprit medication
- When uncertain of a definitive diagnosis, or if patients are unresponsive to therapy, pharmacists should refer patients for further assessment and workup through their general practitioner or dermatologist

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Suggested Resources

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Part III

Chronic Illnesses Assessment

Diabetes Mellitus

12

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Chapter Objectives

1. Describe the diagnostic criteria and tests for diabetes.
2. Describe glycemic control targets for different populations with diabetes.
3. Describe treatment options for patients with diabetes.
4. Apply various tests to assess glycemic control.
5. Describe hypoglycemia, its symptoms and its treatment, and how to avoid it.

Background

Diabetes mellitus is a group of metabolic diseases characterized by elevated blood glucose levels (hyperglycemia) which could be caused by flaws in the secretion of insulin, its action, or both [1, 2]. Around 6% of the world population were living with diabetes in 2014 [3]. This proportion is expected to reach 10% by 2030 because of the rise in the obesity and physical inactivity levels [4, 5]. Due to its chronic nature and the severe complications associated with it, diabetes carries a health and a financial burden on the affected individuals, their care givers, and society as a whole [5]. Poorly controlled diabetes puts patients at higher risk for microvascular and macrovascular complications [5]. Pharmacists are frontline primary healthcare providers who see patients with diabetes frequently. Their interventions in patients with diabetes are well supported by high-level evidence in the literature. This evidence combined with their interest in caring for patients with diabetes puts them in a key position to join the fight against diabetes.

Diabetes can be divided into:

1. *Type I diabetes*

Accounts for 5–10% of the total diabetes cases and occurs when ß-cells in the pancreas are destructed by a cellular-mediated autoimmune attack or other unknown etiology [2, 5].

2. *Type II diabetes*

Accounts for around 90% of the total diabetes cases [2]. It encompasses insulin resistance and insulin deficiency at varying degrees [2, 5].

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3. *Gestational diabetes*

"*Any degree of glucose intolerance with the onset or first recognition during pregnancy*" [2, 5].

4. *Other specific types of diabetes*

This includes a variety of conditions that are caused by genetics, other diseases, or substance use [2, 5].

Case Finding and Diagnosis

Case Finding

Early identification and management of diabetes can help achieve the treatment targets and delay/prevent long-term complications [5]. The patient identification process can be time consuming and frustrating because of the poor yield when healthcare professionals use traditional screening methods [6]. Screening methods include applying tests to entire populations to determine prevalence or probability that the individual will have a disease regardless of the presence or absence of risk factors [6]. In order to improve the yield and the patient identification process as a whole, case finding (a focused approach) is suggested. This is a targeted approach using demographics, risk factors, and/or symptoms to decide whether to apply a test or proceed with further testing [6].

Type I Diabetes

Due to the lack of evidence for type I diabetes prevention and the fact that various serological biomarkers are not widely available, general screening recommendations cannot be made [5]. However, family history of type I diabetes (with special attention to the sex of the family member and their age at onset) can help in estimating the risk of developing type I diabetes [7].

Type II Diabetes

All individuals who are 40 years or older should be assessed using fasting plasma glucose (FPG) or glycated hemoglobin (A1C) every 3 years [8]. The same recommendation applies for those who are at high risk of developing diabetes using a risk assessment calculator. The Canadian Diabetes Risk Assessment Questionnaire (CANRISK) has been validated for assessing diabetes risk in Canada [9]. More frequent and/or earlier testing, using FPG, A1C, or two-hour plasma glucose (2hPG) in a 75 g oral glucose tolerance test (OGTT), should be considered in individuals who are at a very high risk of developing diabetes using a risk assessment calculator or those who have at least one of the following risk factors [5]:

- History of
  - Prediabetes
  - Gestational diabetes
  - Delivering macrosomic infants
- Elements of metabolic syndrome (see below)
- Medications or conditions associated with hyperglycemia (e.g., statins, glucocorticoids)
- End organ damage associated with diabetes (micro- and macrovascular complications)
- Members of high-risk population
  - Indigenous
  - Hispanic
  - South Asian
  - African
  - Asian

Diagnosis

The following tests are used as the diagnostic criteria for diabetes [2, 5]:

1. FPG (no caloric intake for at least 8 hours)
2. 2hPG in a 75 g OGTT
   - Plasma glucose concentration is measured 2 hours after taking a glucose solution (75 g anhydrous glucose dissolved in water)
3. A1C (a measurement of the average glucose control over the previous 3 months)

According to the result of the aforementioned tests, individuals can be classified as outlined in Table 12.1 [2, 5].

Table 12.1 Diagnostic tests results classification [2, 5]

Test result	FPG (mmol/l)	2hPG (mmol/l)	A1C (%)
Normal	≤6	<7.8	<6
Prediabetes	6.1–7	7.8–11.1	6–6.4
Diabetes	≥7	≥11.1	≥6.5

2hPG two hours plasma glucose, *A1C* glycated hemoglobin, *FPG* fasting plasma glucose

Prediabetes refers to individuals with impaired fasting glucose (IFG) (6.1–7 mmol/l), impaired glucose tolerance (IGT) (7.8–11.1 mmol/l), and/or A1C between 6% and 6.4% [5]. Individuals with prediabetes are at high risk of developing diabetes and its complications. As such, they could benefit from cardiovascular (CV) risk factor modification [5]. Prediabetes usually occurs in the context of the metabolic syndrome, a multifaceted condition that is characterized by a group of abnormalities which include elevated lipid levels, elevated blood pressure, and abdominal obesity [5]. Metabolic syndrome is defined as having at least three of the following disorders [10]:

1. Elevated waist circumference, depending on the patient's ethnicity:
   - Canada, United States: ≥ 88 cm for females and ≥102 cm in males
   - Europe, Middle East, Sub Sahara Africa, and Mediterranean ≥80 cm for females and ≥ 94 cm in males
   - Asia and South and Central America ≥80 cm for females and ≥90 cm in males
2. Blood pressure ≥ 130 mm Hg systolic and/or ≥ 85 mm Hg diastolic
3. Fasting plasma glucose ≥5.6 mmol/l
4. Serum triglycerides ≥1.7 mmol/l
5. HDL < 1.3 mmol/l in females and <1 mmol/l in males

The decision of which diabetes diagnostic test to use is up to the clinician's judgement [5]. If the results of two of the tests are available and are indicating diabetes then the diagnosis is confirmed [5]. While, if the individual had no symptoms of hyperglycemia but only one test result was indicating diabetes, then that test should be repeated on another day to confirm the diagnosis [5]. If the random plasma glucose (any time of the day without considering the time since the last meal) test result was ≥11.1 mmol/l but the individual had no hyperglycemia symptoms, an alternate test (FPG, 2hPG, or A1C) is required to confirm the diagnosis [5]. Figure 12.1 illustrates the case finding and diagnosis algorithm for type II diabetes [5].

Management

Type I Diabetes

Insulin should be started at the day of diagnosis for patients with type I diabetes [5]. Table 12.2 lists the types of insulin based on their onset of action [5]. Insulin can be divided into **basal** (refers to intermediate or long-acting insulins which provides glucose control in the fasting state and between meals) and **bolus** (refers to rapid or short-acting insulins which is administered to control the glucose rise after meals or correct hyperglycemia) [5].

Insulin regimens should be individualized based on age, general health, lifestyle, diet, hypoglycemia awareness, ability for self-management, adherence, and social and financial aspects [5]. The most successful insulin regimens for managing type I diabetes are those that combine basal and bolus insulin. Such regimens attempt to mimic the pancreas' normal activity in a person without diabetes [5].

Bolus insulin dose may vary between meals depending on the carbohydrate intake and glycemic index (a scale that ranks carbohydrate-rich foods by how much they raise blood glucose levels compared to a standard food), exercise, time since the last insulin dose, and blood glucose levels [5]. Injections of rapid-acting insulin analogues before meals resulted in lower glucose levels after meals and improved overall glycemic control [11–14]. Faster-acting insulin aspart can be administered at the start of the meal or up to 20 minutes after the start if necessary [15]. The rest of the rapid-acting insulin analogues should be administered 0–15 minutes before starting the meal, while short-acting insulins should be administered 30–45 minutes before the meal [5].

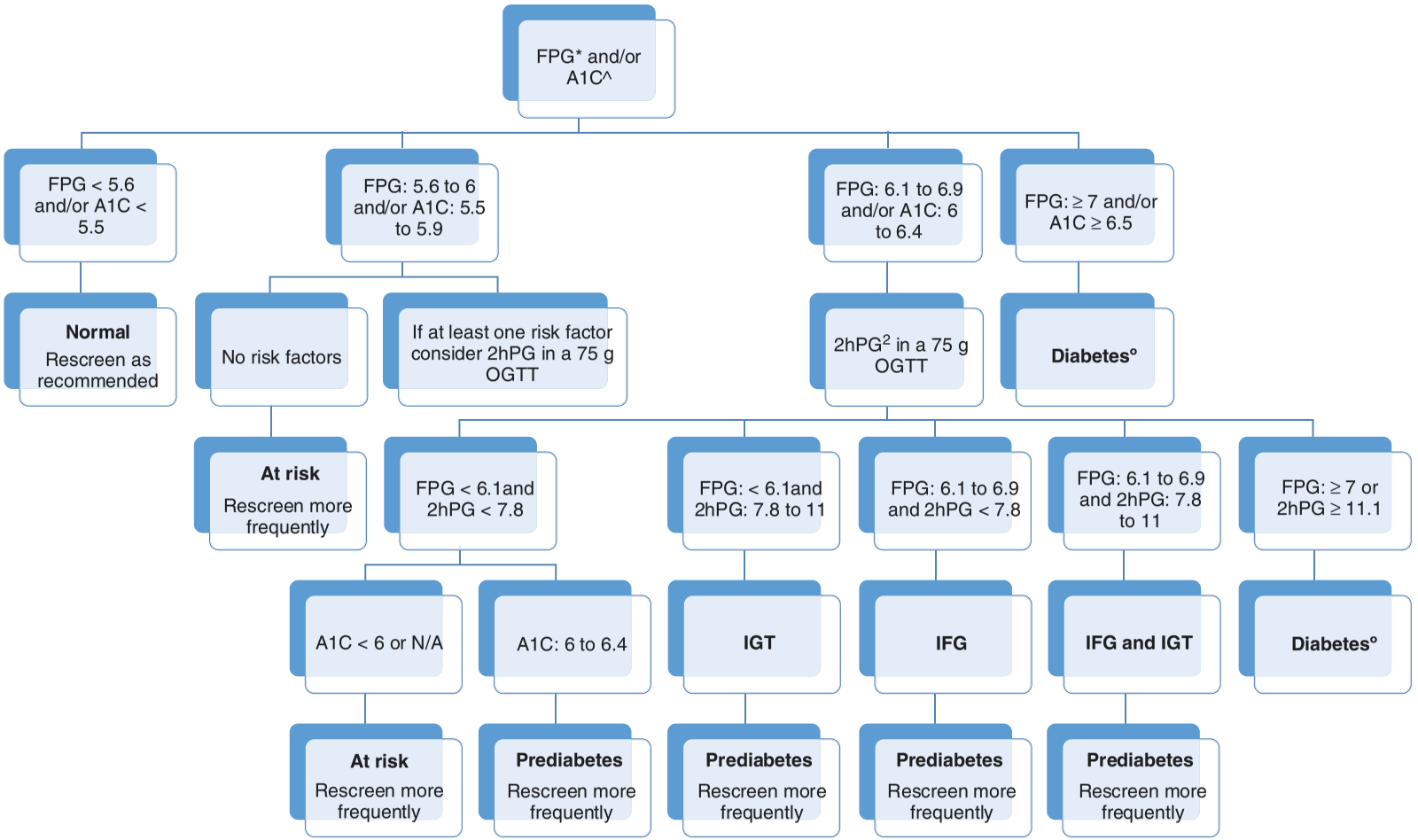


Fig. 12.1 Case finding and diagnosis algorithm for type II diabetes [5]. *FPG's unit is mmol/l, ^A1C's unit is %, [a]2hPG's unit is mmol/l. °If the individual had no symptoms of hyperglycemia but one test result was indicating diabetes, the test should be repeated on another day to confirm the diagnosis. 2hPG two hours plasma glucose, A1C glycated hemoglobin, FPG fasting plasma glucose, IFG impaired fasting glucose, IGT impaired glucose tolerance, N/A not available

Table 12.2 Insulin types based on their onset of action

Onset of action	Insulin
Rapid-acting insulin analogues	Lispro
	Aspart
	Glulisine
	Faster-acting insulin aspart
Short-acting insulins	Novolin® ge Toronto
	Humulin®-R
	Entuzity® (U-500)
Intermediate-acting insulins	Humulin®-N
	Novolin® ge NPH
Long-acting insulins	Glargine U-100
	Glargine U-300
	Glargine biosimilar
	Detemir
	Degludec U-100
	Degludec U-200
Premixed insulins	Humulin® 30/70
	Novolin® ge 30/70, 40/60, 50/50
	Biphasic insulin aspart
	Insulin lispro/lispro protamine

When compared to short-acting insulin, insulin aspart and lispro have been associated with improved glucose control after meals, A1C [14, 16] and quality of life [17], and reduced nocturnal hypoglycemia [14, 16]. It has been reported that insulin glulisine is most effective when given before meals and is equivalent to insulin lispro in glycemic control [11, 18]. When compared to insulin aspart, faster-acting insulin aspart had an earlier onset of action and showed superior glucose control after meals and non-inferior A1C reduction in patients with type I diabetes [15].

When combined with bolus insulin, insulin detemir and insulin glargine (U-100) were associated with better glycemic control and less hypoglycemia (including nocturnal) when compared to neutral protamine Hagedorn (NPH) insulin (once or twice daily) [19–26]. It has been reported that biosimilar glargine (same amino acid sequence but produced in a different process than glargine) had similar efficacy and safety outcomes in adults with type I diabetes who were switched from insulin glargine (U-100) [27]. When compared to insulin glargine (U-100), insulin glargine (U-300) had consistent, gradual, and extended flat release from subcutaneous tissues, longer duration of action (>30 hours), similar effect on A1C and hypoglycemia (one study reported less nocturnal hypoglycemia), and less weight gain [28–32]. When compared to insulin glargine and insulin detemir, insulin degludec had longer duration of action (42 hours), similar glycemic control, lower nocturnal hypoglycemia, and less basal and total insulin dose [29–40]. Degludec (U-100) and (U-200) have similar glucose control effects and half-lives (29).

The choice of insulin regimen should be accompanied with ongoing comprehensive education about caring for and using insulin; self-monitoring blood glucose (SMBG); preventing, recognizing, and treating hypoglycemia; adjusting food intake and exercise; and managing diabetes on sick days [5].

Type II Diabetes

Type II diabetes treatment regimens and glycemic targets should be individualized [5]. Such treatment regimens should aim to avoid and treat hyperglycemia and reduce the risk of microvascular and microvascular complications [41].

A1C Target

While a target of A1C $\leq$ 7% has been recommended for most patients with diabetes [41–44], a stricter target of $\leq$6.5% has been recommended for patients with type II diabetes, who are at low risk for hypoglycemia, in order to reduce their risk of retinopathy and chronic kidney disease (CKD) [44, 45]. A less stringent target of 7.1–8% has been recommended for patients who are functionally dependent to reduce their risk of hypoglycemia and prevent overtreatment. A similar reasoning has been used to justify a target of 7.1–8.5% in patients who have limited life expectancy, a history of severe hypoglycemia, especially if combined with hypoglycemia unawareness and/or frailty with/without dementia [5]. Table 12.3 lists the A1C targets for different populations.

It is important to keep in mind that the treatment targets in the elderly depend on their clinical frailty index [5]. Table 12.4 lists the A1C

Table 12.3 A1C targets for different populations

Population	A1C target
Most adults with type I or type II	≤7%
Adults with type II to reduce the risk of CKD and retinopathy if at low risk of hypoglycemia	≤6.5%
Functionally dependent	7.1–8
History of recurrent severe hypoglycemia	7.1–8.5
Limited life expectancy	7.1–8.5
Frail elderly and or dementia	7.1–8.5
End of life	Measurements are not recommended

A1C glycated hemoglobin, *CKD* chronic kidney disease

Table 12.4 A1C targets in the elderly based on the clinical frailty index

Clinical frailty index	A1C target
Functionally independent (1–3)	≤7%
Functionally dependent (4–5)	7.1–8%
Frail with/without dementia (6–8)	7.1–8.5%
End of life	Measurement not recommended Avoid symptomatic hyperglycemia or any hypoglycemia

A1C glycated hemoglobin

targets in the elderly based on the clinical frailty index.

Agent Choice

Table 12.5 lists all the medication classes and agents that can be used in the management of type II diabetes. The choice of the treatment regimen at the diagnosis of type II should depend on the difference between the patient's A1C and their individual target and the presence of symptomatic hyperglycemia and/or metabolic decompensation [5]:

- If current A1C is <1.5% of the individualized target
  - Healthy lifestyle interventions (exercise, weight management, and healthy eating) with/without metformin should be started
  - If glycemic target is not achieved within 3 months, metformin should be started

Table 12.5 Medication classes used in the management of type II diabetes [5, 46–47]

Medication class	Medications (total adult daily dose)
Biguanide	Metformin (500–2550 mg)
DPP-4 inhibitors	Alogliptin (25 mg) Linagliptin (5 mg) Saxagliptin (5 mg) Sitagliptin (100 mg)
GLP-1 receptor agonists	*Short-acting* Exenatide (10–20 mcg) Lixisenatide (10–20 mcg) *Longer-acting* Dulaglutide (0.75–1.5 mg once a week) Exenatide extended release (2 mg once a week) Liraglutide (0.6–1.8 mg once a day) Semaglutide (0.25–1 mg once a week)
SGLT2 inhibitors	Canagliflozin (100–300 mg) Dapagliflozin (5–10 mg) Empagliflozin (10–25 mg)
Alpha-glucosidase inhibitor	Acarbose (50–300 mg)
Insulin secretagogue Sulfonylureas	Gliclazide (80–320 mg) Gliclazide modified-release (30–120 mg) Glimepiride (1–8 mg) Glyburide (2.5–20 mg)
Insulin secretagogue Meglitinides	Repaglinide (1.5–16 mg)
Thiazolidinedione	Pioglitazone (15–45 mg) Rosiglitazone (4–8 mg)
Rapid-acting insulin analogues	Lispro Aspart Glulisine Faster-acting insulin aspart
Short-acting insulins	Novolin® ge Toronton Humulin®-R Entuzity® (U-500)
Intermediate-acting insulins	Humulin®-N Novolin® ge NPH
Long-acting insulins	Glargine U-100 Glargine U-300 Glargine biosimilar Detemir Degludec U-100 Degludec U-200
Premixed insulins	Humulin® 30/70 Novolin® ge 30/70, 40/60, 50/50 Biphasic insulin aspart Insulin lispro/lispro protamine

DPP-4 inhibitors dipeptidyl peptidase 4 inhibitors, *GLP-1* glucagon-like peptide-1, *SGLT2* sodium-glucose cotransporter 2

(if not initiated already) or its dose should be increased
  - If glycemic target is not achieved within 3 months, a second agent should be added
- If current A1C is ≥1.5 of the individualized target
  - Healthy lifestyle interventions with metformin should be started
    - A second agent could be considered when starting the treatment regimen
  - If glycemic target is not achieved within 3 months, a second agent should be added
- If the patient has symptomatic hyperglycemia and/or metabolic decompensation (dehydration, diabetic ketoacidosis, hyperglycemic hyperosmolar state)
  - Healthy lifestyle interventions with insulin and with/without metformin should be started
  - If glycemic target is not achieved within 3 months, a second agent should be added

If not contraindicated, metformin is considered the first line of treatment in patients with type II diabetes [5]. The presence of clinical cardiovascular disease (CVD) governs the choice of the second line agent [5]. If the patient has clinical CVD, then an agent with demonstrated cardiovascular benefits and that includes empagliflozin, canagliflozin, and liraglutide should be chosen [48–50]. If the patient does not have clinical CVD, The choice of the second line agent should consider the patient's medical history, social and work factors, their preferences and values, and the agent's characteristics [5]. Table 12.6 lists the second line classes and the effects that could impact their choice in the treatment. Table 12.7 summarizes the renal dosage adjustment of antihyperglycemic agents.

The choice of the second agent should be based on the following considerations [5]:

- *The presence/absence of clinical CVD* [5]
- Avoiding hypoglycemia
- Avoiding weight gain (in overweight patients)
- Adequate glycemic efficacy
- Patient values and preferences
- Level of kidney function (based on eGFR)
- Co-morbidities
- Cost, availability, and coverage
- Planning pregnancy

Assessment of Patients with Diabetes

It is important to remember not to be solely glucocentric (focused only on blood glucose management) when managing patients with diabetes [51]. The "*ABCDES*" approach [52] can help to address all aspects of CV risk. This includes assessing A1C, blood pressure, cholesterol, drugs for CVD reduction, exercise/eating, screening for complications, smoking cessation, and self-management [52]. Table 12.8 lists the "*ABCDES*" of diabetes care.

Adherence

Patient's adherence to treatment regimen should monitored and assessed at each encounter with the healthcare professional [53]. Such close monitoring can help answer questions/concerns that patients may have about the disease, the treatment regimen, and the complications [54]. Patients reported that they appreciated receiving such care and compassion [55].

Certain medications should be withheld in periods of acute illness [56]. The abbreviation SADMANS has been used to refer to those medication classes [56]. This includes **S**ulfonylureas, ACE-inhibitors, **D**iuretics, **D**irect renin inhibitors, **M**etformin, **A**ngiotensin receptor blockers, **N**onsteroidal anti-inflammatory drugs, and **S**GLT2 inhibitors [56].

Control and Monitoring

A1C

A1C is a measurement of the average glucose control over the previous 3 months [57]. As such, it is used as an indicator for the treatment effectiveness [5]. A1C should be tested regularly (at least every 3 months) when treatment targets are

Table 12.6 Second-line classes and the effects that could impact their choice in the treatment in type II diabetes

Effect	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors	Alpha-glucosidase inhibitor	Sulfonylureas	Meglitinides	Thiazolidinedione	Insulin
Cardiovascular outcomes	Neutral	CV benefit: Liraglutide Semaglutide Neutral: Exenatide extended-releases, Lixisenatide	CV benefit: Canagliflozin and empagliflozin					Neutral: Glargine Degludec (non-inferior to glargine)
Hypoglycemia	Rare	Rare	Rare	Rare	Yes	Yes	Rare	Yes
Weight	Neutral	Weight loss	Weight loss	Neutral	Weight gain	Weight gain	Weight gain	Weight gain
Glycemic efficacy*	Moderate	Moderate to high	Moderate to high	Mild	Moderate	Moderate	Moderate	Moderate to very high
Other considerations^	- Rare joint pain - Caution with saxagliptin and heart failure	- Subcutaneous injection - GI adverse events - Cases of gallstone disease - Contraindicated with personal/family history of medullary thyroid cancer or MEN 2	- Reduced progression of nephropathy and heart failure hospitalization with empagliflozin and canagliflozin in those with clinical CVD - Genital and urinary tract infections - Hypotension - Dose-related changes in LDL-C - Rare cases of diabetic ketoacidosis (which may occur without hyperglycemia) - Caution with renal dysfunction, loop diuretics, and the elderly - Increased risk of fractures and lower extremity amputation (avoid if prior amputation) with canagliflozin - Dapagliflozin not to be used with bladder cancer	- Common GI adverse events - Requires 3 times daily dosing - Requires using glucose if hypoglycemia occurs	- Relatively rapid blood glucose lowering - Glyburide associated with more hypoglycemia than gliclazide and glimepiride	- Reduced postprandial glycemia but usually requires 3–4 times daily dosing - Repaglinide contraindicated when co-administered with clopidogrel or with gemfibrozil	- Require 6–12 weeks for maximal effect - Mild increase in HDL-C - May induce edema and/or congestive heart failure - Rare occurrence of macular edema - Higher occurrence of fractures - Pioglitazone not to be used with bladder cancer - Controversy regarding MI risk for rosiglitazone	- Subcutaneous injection - No dose ceiling - Flexible regimens

DPP-4 inhibitors dipeptidyl peptidase 4 inhibitors, *GLP-1* glucagon-like peptide-1, *SGLT2* sodium-glucose cotransporter 2

*When added to metformin

^See Table 12.7 for renal dose adjustment

Table 12.7 Renal dosage adjustment of antihyperglycemic agents

eGFR (ml/min)	Medication use		
	No dose adjustment	Reduce dose	Use alternative agent
≥60	Dose adjustment not necessary		
45–59 CKD 3A	Acarbose, Metformin, Linagliptin, Dulaglutide, Exenatide (caution when eGFR <50), Liraglutide, Lixisenatide, Gliclazide (caution), Glimepiride (caution), Repaglinide, TZDs (caution), Insulins	Alogliptin (12.5 md daily), [eGFR <50 Saxagliptin (2.5 mg daily), Sitagliptin (50 mg daily)], Canagliflozin (100 mg daily, do not initiate), Empagliflozin (do not initiate)	Glyburide, Dapagliflozin
30–44 CKD 3B	Acarbose, Linagliptin, Dulaglutide, Exenatide (caution), Liraglutide, Lixisenatide, Gliclazide (caution), Glimepiride (caution), Repaglinide, TZDs (caution), Insulins	Metformin (500–100 mg daily), Alogliptin (12.5 md daily), Saxagliptin (2.5 mg daily), Sitagliptin (50 mg daily)	Glyburide, Canagliflozin, Dapagliflozin, Empagliflozin
15–29 CKD 4	Linagliptin, Dulaglutide, Liraglutide, Repaglinide (caution), TZDs (caution), Insulins (caution)	Alogliptin (6.25 md daily), Saxagliptin (2.5 mg daily), Sitagliptin (25 mg daily)	Acarbose, Metformin, Exenatide, Lixisenatide, Gliclazide, Glimepiride, Glyburide, Canagliflozin, Dapagliflozin, Empagliflozin
<15 or dialysis CKD 5	Linagliptin (caution), Dulaglutide (caution), Repaglinide (caution), TZDs (caution), Insulins (caution)	Alogliptin (6.25 md daily), Sitagliptin (25 mg daily)	Acarbose, Metformin, Saxagliptin, Exenatide, Liraglutide, Lixisenatide, Gliclazide, Glimepiride, Glyburide, Canagliflozin, Dapagliflozin, Empagliflozin

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *TZD* thiazolidinedione

Table 12.8 The ABCDES of diabetes care [52]

		Assessment
A	A1C	Assess A1C level (see individual targets above) Assess hypoglycemia and driving safety if patient is on insulin or insulin secretagogue
B	Blood pressure	Assess BP (target <130/80) Assess the risk of falls if patient is on treatment
C	Cholesterol	Assess LDL (target <2.0 mmol/L)
D	Drugs for CVD reduction	If patient has CVD, use ACE-inhibitor/ARB, statin, and ASA (if A1C is not at target use antihyperglycemic agents with demonstrated cardiovascular benefits) If patient has diabetes complications, use ACE-inhibitor/ARB and statin. If patient is ≥40 years and has type II diabetes, use statin If patient is ≥55 years and has risk factors, use ACE-inhibitor/ARB
E	Exercise and eating	Assess diet (target: healthy diets) Assess exercise (target: 150 minutes of moderate-vigorous exercise per week and 2–3 times per week of resistance exercise)
S	Screening for complications	Assess heart using ECG every 3–5 years if patient is >40 years or has diabetes complications Assess feet using microfilament/vibration every year or more frequently if there are any abnormalities Assess kidney function and status (eGFR and ACR) every year or more frequently if there are any abnormalities Assess eyes using dilated retinal exam every year or more frequently if there are any abnormalities
S	Smoking cessation	Ask permission to support, give advice, and provide therapy to help the patient quit
S	Self-management	Assess for all aspects that can prevent patient from achieving their goals, e.g., cost/coverage, mental health, stress

A1C glycated hemoglobin, *ACE* angiotensin converting enzyme, *ACR* random urine albumin/creatinine ratio, *ARB* angiotensin II receptor blocker, *BP* blood pressure, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate

not achieved or when the treatment regimen is being changed [5]. Target A1C should be attained within 3–6 months of initiating or adjusting the treatment regimen [5].

Blood Glucose Monitoring

Self-monitoring blood glucose (SMBG), flash glucose monitoring (FGM), and continuous glucose monitoring (CGM) are measures that provide information about glycemic control [5]. When dispensing a glucometer or testing strips, it is vital to make sure that the patient is capable of testing their blood glucose successfully [54]. SMBG frequency should be individualized based on the diabetes type, treatment regimen (including diabetes treatment or medications that could affect glycemic control), glycemic control, proneness and awareness to hypoglycemia, and acute illness [5]. Information about prandial glucose control can be obtained with testing before and after the same meal, while bedtime to morning testing will provide information on basal control [58].

Kidney Function and Status Assessment

Monitoring kidney function and status plays an essential role in diabetes treatment, as it could affect the treatment regimen and the medication doses [59]. Indeed, it has been reported that pharmacists ordering kidney function and status tests [eGFR and random urine albumin/creatinine ratio (ACR)] helped uncover a high percentage of unrecognized chronic kidney disease [60].

Treatment decisions should not be made solely based on one kidney function test result, as it could be affected by certain medications (e.g., fenofibrates), conditions (kidney injury, amputation), or diet (high protein diet) [61].

Hypoglycemia

Hypoglycemia is defined as a combination of low plasma glucose level (<4 mmol/l), presence of neuroglycemic (difficulty concentrating, speaking, confusion, headache, dizziness, weakness, drowsiness, and vision changes) or neurogenic (sweating, hunger, trembling, palpitations, nausea, tingling, and anxiety) symptoms, and symptoms that respond to treatment (administration of carbohydrate) [5, 62]. Depending on the severity, hypoglycemia can be divided into [5] the following:

- Mild: The patient will be able to self-treat the neurogenic symptoms
- Moderate: The patient will be able to self-treat the neurogenic and neuroglycemic symptoms
- Severe: Plasma glucose is usually <2.8 mmol/l. Patient usually needs assistance from another person as they may be unconscious

It is essential to try to avoid hypoglycemia, especially in those who are more prone to hypoglycemia [5]. Testing plasma glucose is recommended, when possible, to confirm hypoglycemia and prevent overtreatment [5]. Treatment should be based on the severity of hypoglycemia [5]:

- Mild to moderate: 15 g of carbohydrates (15 g glucose tablets, 150 ml of juice or soft (non-diet) drink, 15 ml (1 tablespoon) of honey, 5 cubes of sugar, 6 Lifesavers ™
  - Plasma glucose should be tested within 15 minutes, if plasma glucose is still <4 mmol/l another 15 g of carbohydrate should be administered
- Severe (conscious patient): 20 g of carbohydrate preferably as glucose tablets or equivalent
  - Plasma glucose should be tested within 15 minutes, if plasma glucose is still <4 mmol/l another 15 g of carbohydrate should be administered
- Severe (unconscious): If there is intravenous access, 10–25 g of glucose should be given intravenously over 1–3 minutes. Glucagon (1 mg) should be given subcutaneously or intramuscularly if there is no intravenous access. Emergency services should be called. Patient should discuss this episode with the healthcare team

The patient should have a meal or a snack once hypoglycemia is reversed. If the next meal is more than an hour away the patient should have a snack that includes a protein source and 15 g of glucose

[5]. Individuals who are on agents that may cause hypoglycemia (e.g., insulin, insulin secretagogues) should be educated about hypoglycemia prevention, recognition, and treatment [5]. Such education should be revisited regularly [5]. Patients should also be educated about driving instructions to make sure that they are not posing risks on the others or themselves [54].

Complications

Poorly controlled diabetes can lead to injury to vasculature [63]. Damage to the large blood vessels may lead to macrovascular complications, while microvascular complications may occur if the damage occurs to the small blood vessels [63]. Macrovascular complications include cardiovascular diseases such as heart attack and stroke, while retinopathy, nephropathy, and neuropathy are considered microvascular complications [64]. See Table 12.8 for the frequency of assessment for complications.

Advise for Patients with Diabetes

Foot Care

Patients with diabetes should do the following foot care activities every day [65]:

- Check their feet for cuts, cracks, bruises, blisters, sores, infections, or any unusual markings
- Apply skin lotion on heals and toes and wipe out excess lotion
- Change socks

They should also trim their toe nails straight across and clean any cuts or scratches with mild soap and water and cover with dry dressing. Healthcare professionals should be contacted immediately if there is pain, swelling, warmth, or redness [65]. Patients are advised wear comfortable and supportive shoes, avoid high heels, buy their shoes in the late afternoon, and avoid extreme temperatures [65].

Vaccination

Patients with diabetes should receive their influenza vaccine every year [5]. They should also get their pneumococcal vaccination if they are 18 years or older and again when they are over 65 years [5]. Herpes zoster vaccine is recommended for individuals who are 60 years or older [5]. All children and those in high-risk groups (does not specify patients with diabetes) for hepatitis B should be vaccinated [5].

Driving

If patients with diabetes are planning on driving they should [5]:

- Measure their blood glucose immediately before driving and every 4 hours on long drives
  - Keep emergency supply of fast-acting carbohydrates
  - Keep supplies of meals and snacks for longer drives and take regular rests
  - Measure more frequently if there are factors that could increase the likelihood of hypoglycemia (e.g., exercise)
- Stop the car in a safe location, if hypoglycemia develops
  - Switch off the car engine
  - Treat hypoglycemia
  - Consider waiting 40 minutes before driving again

Clinical Pearls

- Pharmacists are frontline primary healthcare providers who see patients with diabetes frequently. Their interventions in patients with diabetes are well supported by high-level evidence in the literature. This evidence combined with their interest in caring for patients with diabetes puts them in a key position to join the fight against diabetes
- Before making any decisions, pharmacists should listen to the patient to evaluate their

knowledge and perspective about the situation
- Initial assessment should include a review of the ABCDEs of the patient with the creation of SMART goals and an ACTION plan to help resolve the identified issues
- Pharmacists are encouraged to
  - Assess adherence, glycemic control, hypoglycemia, and any other adverse events or complications during follow-up assessments
    - Follow-up should always include communication within other members of the healthcare team to ensure continuity of care
  - Provide written sick day management instructions so that patients will know which medications to withhold in cases of acute illness
  - Teach about hypoglycemia when appropriate and reinforce regularly
    - Teaching should include
      - Hypoglycemia prevention, symptom recognition, and treatment
      - Driving instructions to make sure that they are not posing risks on others or themselves

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Hypertension

13

Ann Thompson and Peter Hamilton

Chapter Objectives

1. To provide an approach to assessing a patient with hypertension including key patient history information to gather at both initial assessment and follow-up visits.
2. To outline the various methods for assessing blood pressure (BP) and their role in diagnosis and monitoring for those with hypertension.
3. To define thresholds for diagnosing hypertension and target BP once a treatment plan is initiated.
4. To outline appropriate follow-up and monitoring parameters for patients with hypertension.

Background

Hypertension is one of the most common illnesses encountered by Canadians, affecting approximately 25% of adults. The negative impacts of hypertension are increased rates of cardiovascular disease, notably stroke, heart failure, atrial fibrillation, chronic kidney disease and death. Pharmacists, partnering with patients, can assess, educate and help patients better manage this condition through a variety of strategies. This chapter will outline patient assessment considerations to enable pharmacists to provide care to patients with hypertension.

Epidemiology and Etiology

Hypertension is the elevation of systolic or diastolic blood pressure, or both, above normal levels. Hypertension, defined as drug treatment for high BP or BP ≥ 140/90 mmHg, has a high prevalence in Canada and is present in 22.6% of adults [1]. This is a condition most commonly associated with older adults, and those aged 65+ have a prevalence of 50% and this rises with aging. The prevalence of hypertension in diabetics is also high, with 67.1% having hypertension (defined as drug treatment for high BP or BP ≥ 130/80 mmHg). In Canada, despite advances in hypertension management, almost two-third of the patients have their blood pressure within target. Notably, self-reported hypertension prevalence has increased approximately twofold in the last two decades. Despite this, age-standardized mortality rates are falling in hypertensive Canadians (from 9.4 to 7.9 deaths per 1000 individuals) due to improved management and better BP control rates [2].

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Most cases of hypertension are primary, with unknown cause, although this seems to involve increased sympathetic neural activity and increased angiotensin II and aldosterone activity. Secondary hypertension likely accounts for 10–15% of cases. Examples of secondary hypertension include:

- Primary hyperaldosteronism
- Renal artery stenosis
- Chronic obstructive sleep apnoea

Risk Factors

The biggest risk factor for developing hypertension is increasing age, a non-modifiable risk. Once over the age of 65, gender does not seem to make a difference in the prevalence of hypertension. A number of modifiable factors can contribute to hypertension, such as excess salt intake, weight gain and obesity, sedentary lifestyle, obstructive sleep apnoea, select medications (e.g. NSAIDs; corticosteroids; stimulants; select antidepressants, such as monoamine oxidase inhibitors and serotonin and norepinephrine reuptake inhibitors; cyclosporine; oral contraceptives and sex hormones) and other substances (excess alcohol intake, licorice root, stimulants such as cocaine).

Presentation

Typically, hypertension has an asymptomatic presentation (30–40%) and is identified by routine measurement of BP. While hypertension is commonly believed to be one of the causes of headaches, the correlation is not established. One study evaluated the prevalence of headache in those with hypertension using office and 24-hour ambulatory BP measurement. There was no difference in the prevalence of headaches, migraines or analgesics use between subjects who were hypertensive and normotensive. Given the prevalence of both headache and hypertension, it is difficult to establish causality [3]. In another cohort study assessing symptoms of those taking and not-taking antihypertensive therapy, symptoms reported most commonly by patients not taking therapy include dizziness (53%), headache (51%), tiredness (51%), palpitations (35%) and nervousness/restlessness (31%). Intensity of these symptoms was generally mild-moderate (e.g. pain due to headache rated as 4/10). If present and linked to hypertension, symptoms may resolve with reduction in BP [4].

Measuring Blood Pressure

The measurement of BP can occur in two places: in-office and out-of-office. Within office or clinician settings, the preferred BP measurement method is with an automated machine, unattended, that takes multiple readings, typically three to five in total. This method is called automated office BP measurement, or AOBP. The less preferred in-office method (for accuracy) is manual or automated measurement done with the clinician present. If manual measurement is performed, the correct technique is outlined by Hypertension Canada: (http://guidelines.hypertension.ca/diagnosis-assessment/supplementary-tables/#suptbl2a) [5].

Out-of-office measurements are now preferred for three reasons. First, it eliminates whitecoat hypertension (which is a phenomenon associated with elevated BP in a clinician setting, with home or out-of-office BP readings that are lower). Second, more readings can be generated over a greater time frame to demonstrate the pattern and temporal trends associated with BP. Last, it reduces clinician measurement error due to inappropriate technique. There are two methods for obtaining out-of-office readings: ambulatory blood pressure measurement (ABPM), typically done over 24 hours, and home blood pressure measurement (HBPM). Ambulatory BP measurement, if available, is the gold standard test for diagnosis of hypertension; however, it is not always readily available and/or may cost money (depending on coverage in local jurisdiction). This test

typically measures BP every 20 minutes during the day and every 30 minutes during sleep hours. Hypertension Canada outlines the recommended technique on their website: http://guidelines.hypertension.ca/diagnosis-assessment/supplementary-tables/#suptbl3

Home BP monitoring, if done properly, is an accurate predictor of the level of BP control (compared to ABPM) and is a very useful to guide decision-making between patients and clinicians.

BP readings are most accurate and have the potential to reduce overtreatment due to measurement error, when the following conditions are met:

- Using a validated electronic device. Hypertension Canada has a list of validated devices on their website at: https://hypertension.ca/hypertension-and-you/managing-hypertension/measuring-blood-pressure/devices/. Accuracy of home monitors can be determined by comparing to a machine of known accuracy. Electronic devices that are not accurate cannot be re-calibrated for accuracy.
- Using the appropriate cuff size as per the manufacturer guidelines. A cuff that is too small can overestimate BP, whereas too large a cuff will underestimate BP.
- Being comfortable prior to measurement (i.e., no acute pain, bladder empty, comfortable temperature).
- Sitting at rest, with back supported, for 5 minutes prior to taking reading. If the back cannot be supported, as is the case with most pharmacy BP measurement kiosks, one study has demonstrated that this does not lead to big differences in BP accuracy (diastolic BP was shown to only increase by approximately 2 mmHg when the back was unsupported, and there was no statistical difference in systolic BP) [6].
- Supporting arm at heart level prior to taking BP.
- Not talking while taking the BP measurement.

The accuracy of home monitors can be checked by comparing readings to those of a machine of known calibration. For BP machines that are inaccurate, there is no mechanism to "fix" them and a new monitor (with the appropriate cuff size) will need to be purchased. Pharmacists can support patients in home BP monitoring by ensuring they have adequate training and know the appropriate technique. They can also provide information about how to interpret BP readings [7].

Treatment Goals: BP Thresholds and Targets

Pharmacologic treatment thresholds in Canada are recommended based on baseline cardiovascular (CV) risk. Table 13.1 outlines BP thresholds to initiate pharmacologic therapy, and BP targets to achieve, if possible [7]. Even if targets are not achieved, there is a significant reduction in the risk of CV events with a 10–15% lowering of BP from baseline.

Table 13.1 Blood pressure (BP) thresholds to initiate pharmacologic therapy and recommended office BP treatment targets

Population	BP thresholds	BP treatment targets
High risk (defined as presence of CVD or subclinical CVD, CKD, estimated CV risk ≥15%, or age ≥ 75)	SBP ≥ 130 mmHg	SBP ≤ 120 mmHg (based on AOBP)
Diabetes	≥130/80	≤130/80
Moderate risk (according to a CV risk estimation calculator)	≥140/90	≤140/90 *≤135/85 if using AOBP
Low risk (defined as no target organ damage and low risk according to a CV risk estimation calculator)	≥160/100	≤140/90 * ≤135/85 if using AOBP

*BP target if the method of AOBP is used

BP blood pressure, *CVD* cardiovascular disease, *CKD* chronic kidney disease, *SBP* systolic blood pressure, *AOBP* automated office blood pressure

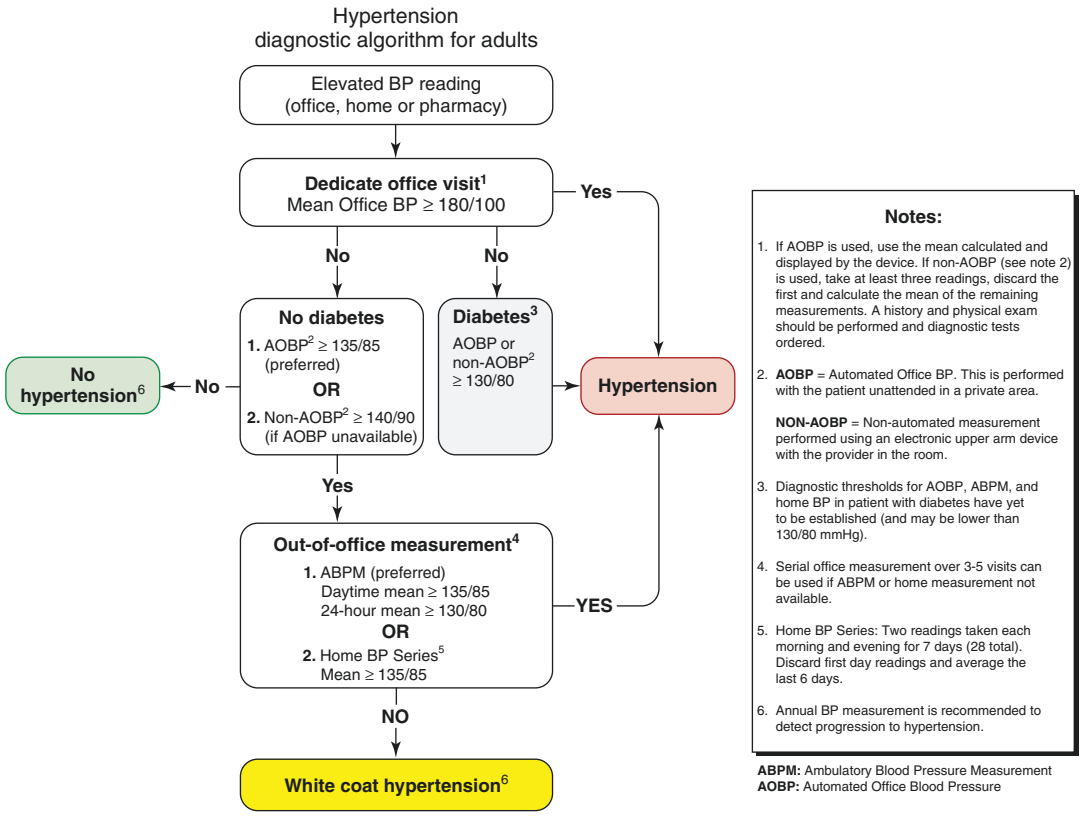


Fig. 13.1 Hypertension diagnostic algorithm for adults. ABPM, ambulatory blood pressure monitoring; AOBP, automated office blood pressure; BP, blood pressure. (Reprinted from Nerenberg et al. [7], Copyright 2018, with permission from Elsevier)

Diagnosis

For persons presenting with features of hypertensive urgency or emergency, or if BP exceeds 180/110, then the diagnosis of hypertension is confirmed, and immediate treatment and ongoing monitoring is required. For all others, the diagnosis of hypertension is best made using out-of-office BP measurements. Figure 13.1 depicts the current diagnostic algorithm as outlined in the Canadian hypertension guidelines [7].

Management

Behaviour modification is a cornerstone to the treatment and prevention of hypertension. Recommendations include:

1. Sodium reduction, to a level not exceeding 2 g sodium per day. Even if this goal cannot be achieved, reductions in dietary sodium have been unequivocally shown to decrease BP. Sodium restriction also enhances the hypotensive effect of diuretics and reduces urinary loss of potassium.
2. Moderate to intense exercise for at least 30 minutes most days of the week (and at a minimum, 4 days weekly).
3. Weight loss to achieve a healthy body weight, if required. Reducing central adiposity is a goal.
4. Alcohol consumption should not exceed 1–2 drinks per day. The weekly maximum is 14 drinks for men and 9 drinks for women.

Pharmacologic treatment is instituted when the benefits of treatment are anticipated to exceed the

Table 13.2 Classes of drugs typically used in the management of primary hypertension

Drug class	Drug names (select)
Thiazide diuretics (* agents with longer duration)	Indapamide* 1.25–2.5 mg daily Chlorthalidone* 12.5–25 mg daily Hydrochlorothiazide 12.5–25 mg daily
Angiotensin converting enzyme inhibitors (ACEi)	Perindopril 2–8 mg daily Lisinopril 5–40 mg daily Ramipril 2.5–10 mg daily Enalapril 2.5–20 mg daily
Angiotensin receptor blockers (ARBs)	Telmisartan 40–80 mg daily Candesartan 8–32 mg daily Irbesartan 150–300 mg daily Valsartan 80–320 mg daily
Dihydropyridine calcium channel blockers (DHP-CCBs)	Amlodipine 2.5–10 mg daily Nifedipine XL 20–120 mg daily
Non-dihydropyridine calcium channel blockers (NDHP-CCBs)	Diltiazem-extended release 180–360 mg daily Verapamil-extended release 120–360 mg daily

*BP target if the method of AOBP is used

harms associated with therapy. There are many antihypertensive drugs to choose from (Table 13.2), and Hypertension Canada outlines treatment strategies based on uncomplicated hypertension or hypertension with comorbidities (Table 13.3) [7].

Initial Assessment of a Patient Newly Diagnosed with Hypertension

Given the prevalence of hypertension, pharmacists are accessible to screen for and educate patients about hypertension. If a patient does not have a diagnosis of hypertension, and high BP readings are detected, pharmacists should work with primary care clinicians to develop an appropriate care plan. An initial assessment by the pharmacist should include the following:

Patient History

(a) History of present illness: Note the course of hypertension and if the patient has ever experienced a hypertensive emergency or urgency, which indicates greater risk for complications of hypertension. Hypertension during pregnancy increases the risk of developing sustained hypertension. Additionally, the longer hypertension has been present (untreated), the likelihood of target organ damage is greater.

(b) Past medical history: History of cardiovascular disease (CVD) and/or target-organ damage (such as microalbuminuria or left ventricular hypertrophy) are prognostic indicators of higher future risk of CVD/complications from hypertension and warrant treatment with pharmacologic therapy in addition to behaviour modification. Consider possibility of secondary causes if BP not easily controlled with behaviour modification and ≥3 medications. Most common secondary causes include obesity, renal failure, primary hyperaldosteronism, sleep apnoea, renal artery stenosis and excessive alcohol use.

(c) Age of onset: Younger onset leads to greater cumulative risk. Patients with a family history of premature hypertension in one parent (defined as onset < age 55) have a two- to threefold increase in risk of developing hypertension, and if both parents had premature hypertension, the risk can be up to 20-fold for developing hypertension.

(d) Cardiovascular (CV) risk assessment if CVD or target organ damage are not already present to determine global CV risk and ascertain BP threshold for treatment and BP target. CV risk assessment can be performed using a variety of risk calculators. One on-line CV risk/benefit calculator is available at http://chd.bestsciencemedicine.com/calc2.html and includes four different calculators for the absolute risk of CVD. One benefit of these calculators is that they provide the clinician and patient with estimates of the benefits and risks associated with different treatment options.

(e) Social history: alcohol and tobacco use, diet (with focus on sodium intake), drug coverage and stress levels.

Table 13.3 Considerations in the individualization of pharmacological therapy in adults[a]

	Initial therapy	Second-line therapy	Notes and/or cautions
Hypertension without other compelling indications			
Diastolic hypertension with or without systolic hypertension	Monotherapy or SPC. Recommended monotherapy choices include thiazide/thiazide-like diuretics (with longer-acting diuretics preferred), β-blockers, ACE inhibitors, ARBs, or long-acting CCBs. Recommended SPC choices include combinations of an ACE inhibitor with CCB, ARB with CCB, or ACE inhibitor/ARB with a diuretic (consider ASA and statins in selected patients)	Additional use of first-line drugs	Not recommended for monotherapy: α-blockers, β-blockers in those 60 years of age or older, ACE inhibitors in black people. Hypokalaemia should be avoided in those prescribed diuretics. ACE inhibitors, ARBs, and direct renin inhibitors are potential teratogens, and caution is required if prescribing to women with child-bearing potential. Combination of an ACE inhibitor with an ARB is not recommended
Isolated systolic hypertension without other compelling indications	Thiazide/thiazide-like diuretics, ARBs, or long-acting dihydropyridine CCBs	Combinations of first-line drugs	Same as diastolic hypertension with or without systolic hypertension
Diabetes mellitus			
Diabetes mellitus with microalbuminuria,[b] renal disease, cardiovascular disease, or additional cardiovascular risk factors	ACE inhibitors or ARBs	Additional use of a dihydropyridine CCB is preferred over a thiazide/thiazide-like diuretic	A loop diuretic could be considered in hypertensive chronic kidney disease patients with extracellular fluid volume overload
Diabetes mellitus not included in the above category	ACE inhibitors, ARBs, dihydropyridine CCBs, or thiazide/thiazide-like diuretics	Combination of first-line drugs. If combination with ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic	Normal urine microalbumin to creatinine ratio <2.0 mg/mmol
Cardiovascular disease			
Coronary artery disease	ACE inhibitors or ARBs; β-blockers or CCBs for patients with stable angina	When combination therapy is being used for high-risk patients, an ACE inhibitor/dihydropyridine CCB is preferred	Avoid short-acting nifedipine. Combination of an ACE inhibitor with an ARB is specifically not recommended. Exercise caution when lowering SBP to target if DBP is ≤60 mm Hg, especially in patients with LVH
Recent myocardial infarction	β-Blockers and ACE inhibitors (ARBs if ACE inhibitor-intolerant)	Long-acting CCBs if β-blocker contraindicated or not effective	Nondihydropyridine CCBs should not be used with concomitant heart failure

Table 13.3 (continued)

	Initial therapy	Second-line therapy	Notes and/or cautions
Heart failure	ACE inhibitors (ARBs if ACE inhibitor-intolerant) and β-blockers. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be used in addition for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated BNP or NT-proBNP level, or NYHA class II-IV symptoms	ACE inhibitor and ARB combined. Hydralazine/isosorbide dinitrate combination if ACE inhibitor and ARB contraindicated or not tolerated. Thiazide/thiazide-like or loop diuretics are recommended as additive therapy. Dihydropyridine CCBs can also be used.A combined ARB/neprilysin-inhibitor is recommended (in place of an ACE inhibitor or ARB) in symptomatic patients with hypertension and HFrEF while receiving standard guideline-based therapies	Titrate doses of ACE inhibitors and ARBs to those used in clinical trials. Carefully monitor potassium and renal function if combining any of ACE inhibitor, ARB, and/or aldosterone antagonist
Left ventricular hypertrophy	ACE inhibitor, ARB, long-acting CCB, or thiazide/thiazide-like diuretics	Combination of additional agents	Hydralazine and minoxidil should not be used
Past stroke or TIA	ACE inhibitor and a thiazide/thiazide-like diuretic combination	Combination of additional agents	Treatment of hypertension should not be routinely undertaken in acute stroke unless extreme BP elevation. Combination of an ACE inhibitor with an ARB is not recommended
Non-diabetic chronic kidney disease			
Non-diabetic chronic kidney disease with proteinuria[c]	ACE inhibitors (ARBs if ACE inhibitor-intolerant) if there is proteinuria. Diuretics as additive therapy	Combinations of additional agents	Carefully monitor renal function and potassium for those receiving an ACE inhibitor or ARB. Combinations of an ACE inhibitor and ARB are not recommended in patients without proteinuria
Renovascular disease	Does not affect initial treatment recommendations. Atherosclerotic renal artery stenosis should be primarily managed medically, whereas revascularization should be considered for renal fibromuscular dysplasia	Combinations of additional agents	Caution with ACE inhibitors or ARB if bilateral renal artery stenosis or unilateral disease with solitary kidney. Renal artery angioplasty and stenting could be considered for patients with renal artery stenosis and complicated, uncontrolled hypertension

Table 13.3 (continued)

	Initial therapy	Second-line therapy	Notes and/or cautions
Other conditions			
Peripheral arterial disease	Does not affect initial treatment recommendations	Combinations of additional agents	Avoid β-blockers with severe disease
Dyslipidaemia	Does not affect initial treatment recommendations	Combinations of additional agents	–
Overall vascular protection	Statin therapy for patients with ≥3 cardiovascular risk factors or atherosclerotic disease. Low-dose ASA in patients 50 years or older. Advise on smoking cessation and use pharmacotherapy for smoking cessation if indicated	–	Caution should be exercised with the ASA recommendation if BP is not controlled

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *ASA* acetylsalicylic acid, *BNP* brain natriuretic peptide; BP, blood pressure, *CCB* calcium channel blocker, *DBP* diastolic BP, *HFrEF* heart failure with reduced ejection fraction <40%, *LVH* left ventricular hypertrophy, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *NYHA* New York Heart Association, *SBP* systolic BP, *SPC* single pill combination, *TIA* transient ischemic attack

[a]Reprinted from Nerenberg et al. [7], Copyright 2018, with permission from Elsevier

[b]Microalbuminuria is defined as persistent albumin to creatinine ratio >2.0 mg/mmol

[c]Proteinuria is defined as urinary protein >500 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol in 2 of 3 specimens

(f) Medication use: Determine current prescription and non-prescription medication use. Note if any medications are known to increase BP and assess if discontinuation (or dose decrease) is an option. Medications known to increase BP are listed in Table 13.4.

(g) Medication allergy or intolerance history: Determine if any antihypertensive agents have been trialed and not tolerated and document the nature of allergy/intolerance. Consider possibility that intolerance reactions may be related to use of a high dose and assess if there is willingness to trial the agent at a lower dose if felt to be beneficial for BP lowering.

BP Assessment

AOBP is recommended for in-office assessment and, subsequently, obtain out-of-office measurements (if patient willing and able). For patients presenting with hypertensive emergency (e.g. symptoms of acute coronary syndrome, acute left ventricular failure, aortic dissection, stroke), refer for immediate medical attention. Home BP measurement should include two readings taken twice daily (approximately 12 hours apart to inform diurnal pattern of BP) for 7 days. Days 2 to 7 (24 readings in total) are averaged to provide overall level of control, and if discrepancies exist between morning and evening readings, the average for each time point can be calculated. Hypertension Canada has a downloadable BP log (https://hypertension.ca/wp-content/uploads/2017/11/HTC_BloodPressureLog_ENG_PREVIEW-1.pdf) that can be printed and given to patients. It is important that BP is measured using a proper technique. Table 13.5 outlines the impact that improper technique can have on BP measurements [8].

Laboratory Values Assessment

If lab values are not available, advise the patient that these are needed as part of the diagnostic workup for hypertension. In some jurisdictions, pharmacists can order laboratory tests as part of completing a patient assessment.

(a) Review parameters which may impact current and/or the selection of drug therapy, such as serum creatinine and electrolytes.

Table 13.4 Examples of medications that may cause an increase in BP

Antidepressants (monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs)	Calcineurin inhibitors (cyclosporine and tacrolimus)
Corticosteroids	Erythropoietin
Oral contraceptives and sex hormones	Midodrine
Non-steroidal anti-inflammatory drugs (NSAIDs)	Stimulants including cocaine and decongestants (phenylephrine, pseudoephedrine)
Licorice root	Second-generation antipsychotics (e.g. clozapine, olanzapine)

Table 13.5 Factors that can increase blood pressure measurements [8]

Factor	Increase on SBP (mm Hg)	Increase on DBP (mm Hg)
"White coat" reaction: to physician	11–28	3–15
Cuff too small	10	2–8
Legs crossed	8–10	4–5
Talking or active listening	7	8
Arm unsupported	1–7	5–11
"White coat" reaction: to nonphysician	1–22	2–7
Smoking within 30 minutes	6	5

DBP diastolic blood pressure, *SBP* systolic blood pressure

Abnormalities in parameters necessitate physician referral for management.

(b) Check urinalysis for presence of proteinuria.

(c) Review parameters that impact CV risk such as lipids and fasting glucose/A1C.

Referral

Patients could be referred to healthcare practitioners to have relevant diagnostic tests (such as ECG, ECHO, renal ultrasound) ordered and/or assessed (if already done).

Physical Assessment Skills by Pharmacist

Pharmacists should initially assess blood pressure and heart rate. Blood pressure assessment can be done using patient-reported home BP measurements or within the practice setting with preference given to AOBP compared to manual measurement. It could be argued that BP should only be done outside the office, but that may not be possible for some patients, making the use of in-office measurement necessary. Using correct BP technique is important to avoid over- or underestimation of BP. Check for hypotension and orthostatic changes in patients who report a history of dizziness. Orthostatic hypotension is defined as either a drop in systolic BP of ≥20 mmHg or diastolic BP of ≥10 mmHg after 1 minute when a patient goes from supine or seated position to standing position. Make sure the patient has adequate support when standing to minimize risk of fall. Prior to completing the two BP measurements (one seated and one standing), inform the patient that you will be asking for their symptoms during the position transition and, if experienced, the time for resolution. This should be documented in your patient assessment. Secondly, pharmacists can assess extremities looking for peripheral oedema. If present, it should be noted if this is pitting or non-pitting. Pitting oedema is most commonly caused by heart failure, renal disease or venous insufficiency, with non-pitting oedema commonly caused by dihydropyridine calcium channel blockers and possibly NSAIDs (if fluid retention). A physician or nurse practitioner should complete an eye, neck, cardiac and abdominal exam.

Follow-Up Assessments

Adherence

Adherence to antihypertensive therapy is known to be poor (estimated to be 50–70%). Reasons are multifactorial and may include (1) the asymptomatic nature of the condition, (2) drug adverse

effects and/or cost and (3) lack of perceived benefits of treatment. Fortunately, there are strategies to help patients adhere to their treatment plan. These include:

- Using medication regimens that fit the patient's daily routine. Once daily medications improve adherence by simplifying medication taking. Once daily medications also tend to be longer acting, which facilitates BP control.
- Using single pill combination (SPC) tablets to minimize pill burden.
- Using adherence packaging (dosettes, blister packs, e.g.) and electronic adherence aids (e.g. reminders on phone via apps that track BP).
- Promoting home BP monitoring so that patients are more engaged in their BP control and can see the effect of their treatment regimen.
- Monitoring effects of treatment regimen more frequently, especially during first 3 months. Pharmacist call-backs have demonstrated benefits to adherence.
- Pharmacist participation in the management of blood pressure, mainly through prescribing of antihypertensives, up-titration of antihypertensives as required to achieve BP goals and reinforcing the treatment plan through more frequent monitoring.

Adherence should be assessed at each clinician visit so that achieved BP is interpreted in the context of medication-taking behaviour. Not surprisingly, non-adherence is a contributor to poor BP control, and if present, reasons for non-adherence should be explored so that possible solutions can be implemented. Pharmacists should work together with patients to determine the reasons for non-adherence and use open-ended questions to explore how adherence could be improved [9–11].

Blood Pressure Control

At each follow-up visit, including pick-up of refills (if practicing in a community pharmacy), the efficacy of the treatment regimen can be assessed. Key elements of patient assessment include:

- *Efficacy assessment*: The degree of BP control achieved based on patient-specific target can be assessed by reviewing home BP logs. In general, if BP is at or below target 80% of the time, BP control is good. For patients not achieving this, intensification and/or additional therapy is needed. In some cases, this can be achieved by using longer-acting agents that have a more durable BP-lowering effect. Also, if an added treatment does not seem to be contributing to any BP lowering, rather than adding on therapy, it can be substituted for an alternate BP-lowering agent.
- *Safety assessment*: Determine if BP is too low for the individual patient (either persistently or intermittently), as evidenced by BP logs and reports of dizziness/light-headedness and general malaise and/or fatigue. If symptoms present, consider other contributors, such as acute illness or other medical conditions, that may also lead to these symptoms. If hypotension is suspected to be the main cause, encourage more frequent home BP monitoring to correlate symptoms with BP and de-prescribe antihypertensive therapy as required until symptom improvement. Ongoing home BP monitoring will guide future adjustments to the treatment plan.

Box 13.1 depicts an example of a patient assessment.

Adverse Reactions of Hypertension Drug Therapy

While antihypertensive therapies are generally well-tolerated, side effects and/or laboratory abnormalities can emerge, necessitating a change in therapy. For pharmacists working in a community pharmacy setting, adherence can be checked based on refill records, which if poor, may be a clue about poor treatment tolerability. Monitoring is important to check for anticipated possible

Box 13.1 Patient Assessment Using a Home BP Log

The following case illustrates an approach to a patient with hypertension:

A 62-year-old female patient you have been following brings in her home BP log from the last week. She was recently diagnosed with hypertension (BPs often 170–180 mmHg systolic), started on drug therapy and has been recording home BPs. She is asymptomatic, although initially noticed she was urinating more frequently, which has now normalized.

Pertinent Background Details

Chief Complaint: Soliciting your advice on the effectiveness of her drug therapy for hypertension – she thought this drug would normalize her BP.

Past Medical History: Hypertension, treated for 1 month

Social: Drinks about 14 glasses of wine per week (approximately 2 per evening), non-smoker (quit 30 years ago, prior to having her children), obese for ++ years (BMI 40)

Medications: Indapamide 1.25 mg qam (started 4 weeks ago)

Does not use any OTC or herbal products

Behaviour Modifications: Nil

Select Labs (from 2 weeks ago):

Scr normal, urinalysis reveals 1+ proteinuria

K+ 3.6 mmol/L (3.5–5.0) [was 4.0 mmol/L 3 months ago]

Na+ 138 mmol/L (133–146 mmol/L)

BP Log

Date	Day number	Time	Heart rate	BP reading #1		BP reading #2	
				SBP	DBP	SBP	DBP
May 10	Day 1 morning	0655	80	155	95	152	93
	Day 1 evening	1800	85	162	90	160	89
May 11	Day 2 morning	0700	82	157	89	159	92
	Day 2 evening	2200	78	172	88	167	91
May 12	Day 3 morning	0630	91	165	88	165	90
	Day 3 evening	1900	96	168	87	166	89
May 13	Day 4 morning	0605	88	180	92	171	92
	Day 4 evening	1730	86	152	97	158	99
May 14	Day 5 morning	0645	85	170	99	165	96
	Day 5 evening	2230	91	166	95	166	94
May 15	Day 6 morning	0700	88	148	94	152	89
	Day 6 evening	2300	92	146	94	145	92
May 16	Day 7 morning	0640	81	157	96	160	94
	Day 7 evening	2040	83	155	97	154	97

Patient Assessment Approach

Review BP log:

Calculation of average BP, averaging days 2–7 (as per Hypertension Canada guidelines).

Average *morning* BP (12 readings over 6 days) is 162/93.

Average *evening* BP (12 readings over 6 days) is 160/93.

Overall BP control (24 readings over 6 days) is 161/93.

Pulse within normal limits.

Is it required to calculate a morning and evening BP average?

Not necessarily, but patients can have BP that is variable across the day, with one time period seemingly revealing a higher BP. This can influence recommendations to dose antihypertensive

medication(s) at a certain time of day. Upon visual inspection, this BP log reveals similar BPs, regardless of time. When that is the case, an overall average is sufficient (notation can be made indicating that BPs are consistently elevated across the day).

BP measurement assessment (to assess accuracy of BP log)

Is the patient using proper technique to measure BP? Assess the following:

1. Using a monitor that is accurate when measured against one of known calibration?
2. Using an upper arm-based BP cuff, if appropriate size is available? If not, a wrist cuff would be appropriate.
3. Using appropriate set-up prior to measurement? (i.e., putting cuff on arm in appropriate location and tension, sitting with back supported, arm supported at heart level, feet flat on ground, with no crossed legs, not talking, no coffee/tobacco within previous 30 min)

Effectiveness/safety of current treatment

- Taking indapamide for 4 weeks, which is enough time to elicit maximum response. Patient is tolerating and adherent. Urination has subsided.
- Serum potassium has lowered, as expected with thiazide diuretics. It is still within normal range. She has 1+ proteinuria, likely due to uncontrolled hypertension.

Assessment/recommendations

- Home BP monitor is accurate and patient using correct technique.
- BP above target of <135/85; requires additional therapy (many options exist, and using a long-acting, single-pill combination can improve adherence and efficacy).
- Behaviour modification should be discussed, specifically, sodium and weight reduction, exercise, limiting alcohol intake (to nine or less drinks/week, which may be increasing her BP), DASH diet.
- Continue to monitor home BP, especially 3–4 weeks after new medication/behaviour modifications introduced. Measure BP twice daily.

effects, as well as effects that are not anticipated. Table 13.6 outlines the four first-line drug classes and common or anticipated adverse effects as well as management strategies. Fortunately, there are many antihypertensive drug agents available to prescribing clinicians allowing for flexibility to address adverse effects. It is important to work with patients to routinely assess for drug-therapy complications and assure them that other options exist, with the hopes of improving adherence to the prescribed treatment regimen.

Complications of Hypertension

Hypertension is a leading risk factor for disability and death from cardiovascular causes. The potential complications of uncontrolled hypertension are listed below.

Cardiac/vascular

- Left ventricular hypertrophy, atrial dilatation and fibrillation
- Diastolic and systolic heart failure
- Accelerated coronary artery disease, myocardial infarction and systemic atherosclerosis
- Aortic dissection and aneurysm

Renal

- Proteinuria
- Haematuria
- Renal failure

Central nervous system

- Haemorrhagic, lacunar and ischemic stroke
- Posterior reversible encephalopathy syndrome (PRES)
- Seizure
- Vascular dementia

Table 13.6 List of most common drug complications in patients with hypertension

Drug class	Common adverse reactions/ precautions	Management strategy
Thiazide diuretics (* agents with longer duration)	Hypokalaemia (if severe, may present as muscle cramping) Hyponatraemia Hyperuricaemia and hypercalcaemia Hyperglycaemia (in non-DM patients)	Know baseline values. Monitor electrolytes 1–2 weeks after initiation of therapy or dose changes. If baseline K+ < 4 mmol/L, recommend to prescribe in conjunction with an ACEi/ARB (as a SPC) or a potassium-sparing diuretic Lower dose (and do not exceed maximum recommended dose, which can exacerbate adverse reactions) Switch to a different class
Angiotensin converting enzyme inhibitors (ACEi)	Hyperkalaemia (dose-related) Dry cough May cause transient increase in serum creatinine (Scr), which should resolve. Do not use in pregnancy	Reduce dose if possible Prescribe with a thiazide or loop diuretic, which can normalize hyperkalaemia If cough develops, switch to an ARB If Scr increases >30%, refer for investigation of renovascular hypertension
Angiotensin receptor blockers (ARBs)	Hyperkalaemia (dose-related) May cause transient increase in serum creatinine (Scr), which should resolve Do not use in pregnancy	Reduce dose if possible Prescribe with a thiazide or loop diuretic, which can normalize hyperkalaemia If Scr increases >30%, refer for investigation of renovascular hypertension
Dihydropyridine calcium channel blockers (DHP-CCBs)	Pedal oedema bilaterally, non-pitting (dose-dependent)	Reduce dose Adding a venodilator to regimen; most commonly studied is ACEi
Non-dihydropyridine calcium channel blockers (NDHP-CCBs)	Bradycardia (dose-dependent) Pedal oedema bilaterally, non-pitting (dose-dependent)	Monitor heart rate (HR) and reduce dose if <50 or if patient feels unwell/fatigued at higher HR Try dosing at bedtime to minimize pedal oedema

*BP target if the method of AOBP is used

- Retinopathy
- Postural hypotension and syncope

Other

- Erectile dysfunction

Postural hypotension is a risk of treatment, especially if lower BP targets are being attempted. With the publication of the SPRINT and ACCORD trials, SBP < 120 mmHg reduces CVD and is therefore recommended for high-risk patients (on the assumption they tolerate the lower SBP). In the SPRINT trial, the risk of hypotension was higher (about double) in those achieving a SBP target of less than 120 mmHg compared to those achieving a SBP between 130 and 140 mmHg (1.8% vs. 0.8%). Syncope was also increased in patients achieving a SBP < 120 mmHg (1.6% vs. 0.6%). Injurious falls (requiring ER visit or hospitalization) were the same between groups [12]. Pharmacists can play a key role in monitoring patients for hypotension during clinic appointments or when patients pick up refills for antihypertensive medications. Assessment can consist of BP measurements and/or patient history that describes the nature, frequency and duration of hypotensive episodes. Deprescribing antihypertensive drug therapy is appropriate if patients are experiencing symptomatic hypotension.

Clinical Pearls

- Pharmacists can play a key role in assessing patients (both initially and during follow-up) with hypertension to ensure treatment regimens are effective, safe and adhered to. As patient status can change, routine monitoring is important.
- Out-of-office BP measurement is important to monitor BP control. Use this method routinely

to inform and justify changes to treatment regimens.

- Drug therapy must be tailored to ensure maximum effectiveness and minimal side effects. Short acting antihypertensive drugs should be avoided. The use of long-acting drugs, in combination, is preferred.
- The average antihypertensive drug will lower BP by about 10%. If the BP at the onset is well above target, combination therapy can be started.
- Changes to pharmacologic regimens can take up to 3–4 weeks to reach maximum treatment effects, so resist the urge to adjust regimens at intervals that are shorter.
- Use caution when lowering BP in patients with a vascular obstruction such as aortic stenosis or carotid/renal artery stenosis.
- ARB and ACEi are teratogenic and must be used with caution in women of childbearing age.

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Suggested Reading

www.hypertension.ca. Hypertension Canada website, which provides education and recommendations for healthcare professionals, patients and partners about hypertension.

Heart Failure

14

Sheri L. Koshman and Lesley C. Beique

Chapter Objectives

1. To define heart failure (HF)
2. To review the diagnosis of HF including common signs and symptoms, risk factors and common diagnostic tests
3. To highlight goals of therapy in patients with HF
4. To outline a general approach to a patient with HF including initial assessment and ongoing evaluation and monitoring
5. To provide an approach to pharmacotherapy in HF including parameters for initiation and titration of therapy.

Background

Heart failure (HF) is common in Canada with over 600,000 people living with the disease. Every year, approximately 50,000 people are newly diagnosed with HF [1]. Both the prevalence and incidence of heart failure is growing secondary to higher survival post myocardial infarction, better diagnosis and treatments for HF and an aging population. HF is burdensome to the healthcare system, costing an estimated $2.8 billion dollars yearly and is largely driven by hospitalizations.

HF is a complex clinical syndrome in which there is a decrease in cardiac output that results in a decrease in its ability to meet the metabolic demands of the body. It is any structural or functional disorder that impairs ventricular (right or left) filling (diastolic) or ejection (systolic) of blood. The defect can be intrinsic or extrinsic to the heart. It can also present acutely or chronically (Fig. 14.1). It is classified as a syndrome, because regardless of the cause, it presents with a similar group of signs and symptoms. Ejection fraction (EF) is also used to further define HF. HF with preserved ejection fraction (HFpEF) is a patient with an EF > 50% and HF with reduced ejection fraction (HFrEF) is a patient with an EF < 40%. There is also a small subgroup of patients with EF 40–49% called HF with midrange ejection fraction (HFmrEF) as well as those with HF with improved EF. This chapter will focus on the approach to the patient with chronic HFrEF as this subset of HF is most applicable to the majority of pharmacists and the available evidence-based pharmacotherapy. However, the general assessment approach can be applied to the overall syndrome of HF.

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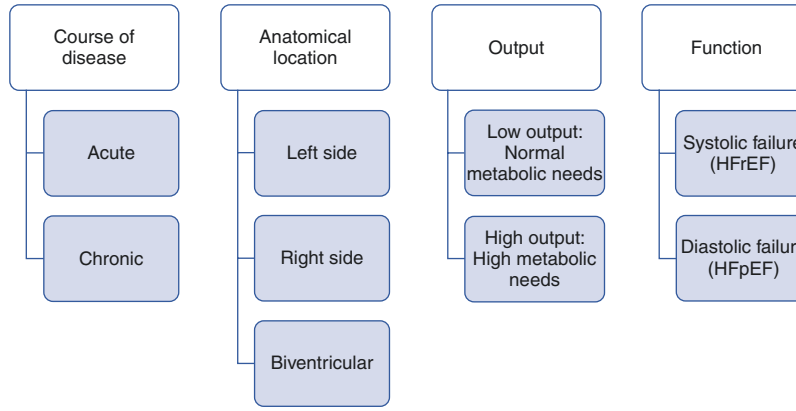


Fig. 14.1 Clinical classification of heart failure

Initial Assessment

The general approach to a HFrEF patient includes the following:

- Assess signs and symptoms of HF to determine baseline and functional capacity
- Assess fluid status
- Determine if there are any risk factors for HF that can be managed
- Determine the need for medical management:
  - Assess any contraindications/allergies
  - Consider any co-morbidities/other factors (other medications, drug interactions, cost, adherence) that might change therapy and doses selected
  - Assess baseline parameters for drug therapy prior to drug initiation/dose selection (e.g., serum creatinine (SCr), potassium, blood pressure (BP), heart rate, ECG abnormalities, etc.)

The case described in Box 14.1 illustrates these points and some other considerations when approaching a patient with HF.

Diagnosis

What information from Mr. Smythe's case do we have that would be used in the diagnosis for HF?

The diagnosis of HF is clinical. It involves taking a careful history, reviewing the signs and symptoms of the patient, performing a physical examination, reviewing risk factors and using diagnostic tests such as blood tests and echocardiography. It is a constellation of these signs and symptoms that leads to a diagnosis of heart failure.

What signs and symptoms do Mr. Smythe have that are consistent with HF?

The most common symptoms (experienced by the patient) of HF including those experienced by Mr. Smythe are depicted in Table 14.1.The most common signs (detected by someone other than the patient) of HF including those present in Mr. Smythe are depicted in Table 14.2. The signs and symptoms may vary among patients and will depend on the acuity of the situation and whether it is right-sided or left-sided HF. It is especially important to note that not all HF involves congestion. Signs and symptoms related to congestion of peripheral tissues (leg swelling, ascites, HJR, elevated JVP) are related to right-sided heart failure, which may occur with left-sided HF or in isolation and can be improved/reversed with fluid management (e.g., diuresis). On the other hand, left-sided HF is characterized by a decrease in cardiac output manifesting as activity intolerance and decreased tissue perfusion and/or pulmonary congestion causing impaired gas exchange (cyanosis/hypoxia) and/or pulmonary edema (cough, orthopnea, paroxysmal nocturnal dyspnea [PND]). If the patient does not have any right-sided HF, they will not have the classic signs of peripheral edema. It is for this reason that HF

Box 14.1 Patient Care

You are the pharmacist in a heart failure clinic. A patient with a recent emergency room visit for heart failure has been referred to the clinic for assessment and treatment. You find the following admission history in the patient chart.

CC: Paul Smythe is a 70-year-old male presenting with worsening SOB and fatigue over the past few months.

HPI: Mr. Smythe has been experiencing increased SOB on exertion for the last 2–3 months. He recalls first noticing his symptoms on his regular morning walk which is about 8 blocks. He began to get "short on air." At first it just made him slow down, but soon it was making him stop after a couple of blocks. He tried taking his puffer with no improvement. About 3 weeks ago, he had to call a taxi to take him home because he was too SOB to continue. It was this time that he decided to go to the ED. He also notices SOB climbing one flight of stairs at home or doing any type of exertion, including things like taking out the garbage or mowing the lawn. He has seen his family doctor a couple of times and received two courses of antibiotics, for a presumed upper respiratory tract infection related to his COPD, without any improvement. Prior to this, he was rarely limited by SOB. He would only notice "mild" SOB if he climbed >2 flights of stairs or was doing heavy lifting. He walked daily and did all his own house and yard work. His main limitation was the pain in his left knee for his arthritis, which he was awaiting replacement surgery.

He also describes being "drained of energy." He reports sleeping poorly and would get SOB any time he tried to lay flat in bed. At one point, he recalls sleeping with four pillows and eventually needing to sleep in his recliner to avoid being SOB. He has noticed swelling in both of his legs, which at one time precluded him from wearing any of his shoes. He describes a poor appetite and notes that even when he is hungry, he gets full quickly and is unable to eat much. Despite this, he reports his pants getting tighter and his weight going up. He has gained ~7 kg over 2 months.

Two weeks ago, he went to the ED because the breathing got so bad. He was given furosemide 40 mg IV × 2 and then oral (40 mg BID) and referred urgently to the Heart Failure Clinic for assessment and treatment. At that time, his ECG reported NSR and his CXR showed pulmonary edema. He was also noted to have 2+ pitting edema to the shin bilaterally. His symptoms have improved since this visit, but he is "nowhere near normal." He can only walk one block without stopping and still requires two pillows to sleep, and the swelling in both of his feet is still present. His weight is down ~3 kg.

He denies chest pain, palpitations, syncope, presyncope or light-headedness. He has a "morning cough" that is productive but has been present and stable since he was diagnosed with COPD. However, he did notice more coughing when he needed to sleep in his recliner.

Past Medical Hx:

HTN × 20 years; has a home BP monitor – 150–160/70–80 mmHg × 1 year; previously 160–180/70–80 mmHg
Dyslipidemia × 6 years
DM2 × 2 years; does not have home monitor
OA of left knee × 12 years
COPD × 4 years; "mild," no hospital admissions

Family Hx: Mother died of MI at 82 years old

Social Hx:

Retired. Widowed. Lives alone in a house; prior to symptoms, able to maintain on own
Smoking: Quit smoking 20 years ago; 40 pack-years
EtOH: 2 drinks per week, never a heavy drinker; Illicit drugs: none
Exercise: walked 30 minutes daily prior to symptoms starting
Diet: 3 meals per day; a lot of prepared frozen dinners; eats out weekly; no added salt
Allergies: NKDA

Medications:
Amlodipine 5 mg PO daily (×15 years)
Hydrochlorothiazide 25 mg PO daily (×10 years)
Atorvastatin 40 mg PO daily (×6 years)
Furosemide 40 mg PO BID (×2 weeks)
Metformin 1000 mg PO BID (×2 years)
Tiotropium 18 μg inhaled daily (×4 years)
Salbutamol 1–2 puffs inhaled QID prn (never uses, other than recently with increasing SOB)
Ibuprofen 200–400 mg PO TID prn (generally uses 400 mg qhs and then prn q2days)

Vital Signs:
BP sitting = 130/80 BP standing = 118/78 HR sitting = 94 HR standing = 100
Ht = 160 cm Wt = 86 kg (Baseline: 78 kg)

Physical Examinations:
RESP: course crackles to the bases bilaterally
CVS: S1, S2, S3, no murmurs, JVP 7 cm above the sternal angle (ASA), + HJR
GI/GU: ascites
MSK: ++ pitting edema to shins bilaterally

Labs:

	1 day ago	1 month ago	6 months ago
Na	132	138	134 mmol/L
K	3.5	3.9	4.4 mmol/L
Cl	104	101	106 mmol/L
SCr	130	98	70 umol/L
Hgb	145	138	140 g/L
WBC	7.0	7.8	7.9×10^9/L
PLT	317	325	330×10^9/L
BNP	2200	–	– pg/ml
TSH	3.00	–	– mU/L

Investigations:
CXR: cardiomegaly, interstitial pulmonary edema
ECG: normal Sinus rhythm, left ventricular hypertrophy, left bundle branch block, QRS 130 msec, NSR, HR = 80 bpm
Cardiac PET Scan: normal perfusion, EF = 35%
Echocardiogram:
Ventricle: Mildly dilated left ventricle, concentric LVH, global LV hypokinesis, EF = 30%, some diastolic impairment
Atria: dilated left atrium
Valves: Aortic valve sclerosis, mild mitral regurgitation

Case abbreviations: BID, twice daily; BNP, B-type natriuretic peptide; BP, blood pressure; CC, chief complaints; Cl, chloride; COPD, chronic obstructive pulmonary disease;CVS, cardiovascular system; CXR, chest X-ray; DM2, diabetes mellitus type 2; ECG, electrocardiography; ED, emergency department; EF, ejection fraction; ETOH, alcohol; GI, gastrointestinal; GU, genitourinary; Hgb, hemoglobin; HJR, hepatojugular reflex; HPI, history of present illness; HTN, hypertension; JVP, jugular venous pressure; K, potassium; LVH, left ventricular hypertrophy; MI, myocardial infarction; MSK, musculoskeletal; Na, sodium; NSR, normal sinus rhythm; OA, osteoarthritis; PET, positron emission tomography; PLT, platelets; QID, four times daily; RESP, respiratory; SCr, serum creatinine; SOB, shortness of breath; TID, three times daily; TSH, thyroid-stimulating hormone; WBC, white blood cells

is no longer called congestive heart failure. Mr. Smythe has many signs and symptoms that are consistent with a clinical diagnosis of HF, many of which are consistent with acute congestion.

Clinical Pearl Shortness of breath can be subjective. Listen carefully to the patient and include questions about daily activities in your assessment. When assessing SOB, establish baseline activity and timelines for the onset/change in symptoms. Always relate activities specifically to ones that the patient regularly performs.

What diagnostic tests did Mr. Smythe have to contribute to the diagnosis of his HF?
Diagnostic tests that add to the clinical diagnosis of HF are shown in Table 14.3. A specific laboratory test that can be used to evaluate HF

Table 14.1 Common symptoms of heart failure

Symptoms	Mr. Smythe	Case-specific examples
Shortness of breath (SOB)	Yes	Change from baseline activity: Walking 8 blocks to 1 blocks Climbing >2 flights of stairs to <1 flight New limitation doing yard work
Cough	Yes	Pre-existing cough but worse with orthopnea
Swelling (leg, abdomen)	Yes	Legs: Swelling in both of his legs, at times precluded wearing shoes Abdomen: Poor appetite, even with hunger, feels full quickly and is unable to eat much (early satiety) Reports pants getting tighter and weight going up (~7 kg in 2 months) despite decrease intake and less activity Weight loss post diuretic treatment (~3 kg)
Orthopnea	Yes	Reports sleeping poorly, SOB any time laid flat in bed Sleeps with 2 pillows, down from 4 pillows/ sleeping in his recliner
Paroxysmal nocturnal dyspnea (PND)	No	–
Fatigue	Yes	Describes being "drained of energy"
Confusion	No	–

Table 14.2 Common signs of heart failure

Sign	Mr. Smythe	Case-specific examples
Lung crackles/rale	Yes	Crackles
Elevated jugular venous pressure (JVP) > 4 cm above the sternal angle (ASA)	Yes	7 cm ASA
Positive hepato-jugular reflex (HJR)	Yes	
Peripheral edema	Yes	2+ pitting edema bilaterally to mid-shin Ascites
Displace cardiac apex	Not noted	
S3, S4 heart sounds	Yes	S3
Tachycardia (HR > 120)	No	
Heart murmur	No	
Low blood pressure	No	
Chest X-ray findings:		
Cardiomegaly	Yes	
Pleural effusion	No	
Pulmonary edema	Yes	
Pulmonary venous redistribution	No	
ECG		
Q waves	No	
Left ventricular hypertrophy (LVH)	Yes	
Left bunch branch block (LBBB)	Yes	
Tachycardia	No	

HR heart rate

Table 14.3 Diagnostic tests that add to the clinical diagnosis of heart failure

Diagnostic tests	Indicates	Mr. Smythe
Chest X-ray findings:		
Cardiomegaly	Possible dilated ventricle	Yes
Pleural effusion	Pulmonary congestion	No
Pulmonary edema	Pulmonary congestion	Yes
Pulmonary venous redistribution	Pulmonary congestion	No
ECG findings		
Q waves	Possible ischemic	No
Left ventricular hypertrophy (LVH)	Possible pressure overload	Yes
Left bunch branch block (LBBB)	Possible dilated ventricle	Yes
Tachycardia	Sympathetic overdrive	No
BNP > 500 pg/ml	Fluid overload causing ventricle to stretch	Yes

BNP B-type natriuretic peptide

is the B-type natriuretic peptide (BNP) or the N-terminal-pro-BNP (NT-proBNP) test. BNP is a hormone released by ventricular cardiomyocytes in response to ventricular stretching caused by increased blood volume. This test has a number of applications (diagnosis, prognosis, therapy decision making etc.), but its most practical everyday clinical application to date is its use as a tool to rule in or out HF if the diagnosis is in doubt (Table 14.4). Based on Mr. Smythe's signs and symptoms, a BNP was not necessary to make a diagnosis of HF (BNP = 2200 pg/ml). However, if his symptoms were inconsistent and

Table 14.4 Levels for BNP and NT-pro-BNP indicating heart failure [2]

BNP	NT-pro-BNP
<100 pg/ml – acute HF decompensation unlikely	<300 pg/mL – acute HF decompensation unlikely
>500 pg/ml – HF likely	>900 pg/mL – HF likely (age 50–75)
	>1800 pg/mL – HF likely (age > 75)

BNP B-type natriuretic peptide, *NT-pro-BNP* N-terminal-pro-BNP

if there was a question that his dyspnea was from a COPD exacerbation (note that he was treated with antibiotics twice for similar symptoms), then a BNP might be helpful in determining the cause of dyspnea.

What tests has Mr. Smythe had that are consistent with a clinical diagnosis of HF?

Because HF is a clinical diagnosis (e.g., based on history, risk factors, signs and symptoms), diagnostic tests, including laboratory parameters, are mainly used to help determine the etiology or confirm clinical suspicion if the diagnosis in unclear (e.g. inconsistent signs and symptoms). Based on Mr. Smythe's history and signs and symptoms, the diagnosis of HF can be made. However, the treatment approach may be different depending on the type of HF present, which would require further evaluation.

The most common diagnostic test used to evaluate the function of the heart is echocardiography, or ultrasound of the heart. This modality can assess the structure of the heart (e.g., valves, muscle thickness, chamber sizes) as well as the function of the heart (e.g., ejection fraction, filling pressure, etc.). There are a number of parameters used in the assessment of a patient with HF, but the most commonly used parameter is the EF, or the ratio of blood ejected from the heart relative to the amount presented to the left ventricular. Other tests that may be used to evaluate a patient with HF and determine etiology might include coronary catheterization, magnetic resonance imaging (MRI), stress testing (exercise stress test, MIBI scan, PET scan, etc.) and other laboratory parameters.

Mr. Smythe's EF is 30%, which is consistent with HFrEF (normal EF $\geq$ 60%). Of note, his results also indicated some diastolic dysfunction, which is common and consistent with his history of hypertension.

Risk Factors and Etiology

Does Mr. Smythe have any risk factors for developing HF?

There are many risk factors for developing heart failure (Table 14.5). Mr. Smythe's risk factors include hypertension, diabetes and use of non-steroidal anti-inflammatory drugs (NSAIDS).

What is the cause of Mr. Smythe's HF?

The most common cause of HF is ischemic heart disease, followed by hypertension and valvular heart disease. Other causes are listed in Table 14.6. Given Mr. Smythe's high risk

Table 14.5 Risk factors for developing heart failure (HF)

Hypertension	Family history of HF
Ischemic heart disease	Smoking
Valvular heart disease	Dyslipidemia
Diabetes	Drugs: NSAID, COX2 inhibitors, thiazolidinediones
Heavy alcohol use	Chemotherapy
Sleep apnea	Obesity

COX cyclooxygenase, *NSAIDs* non-steroidal anti-inflammatory drugs

Table 14.6 Common causes of heart failure

Ischemia cardiomyopathy (36–59%)
Non-ischemic cardiomyopathy
Hypertensive heart disease (4–78%)
Valvular cardiomyopathy (7–31%)
Idiopathic dilated cardiomyopathy
Familial cardiomyopathy
Inflammatory cardiomyopathy: Viral, peripartum
Restrictive cardiomyopathies: Sarcoidosis, hemochromatosis
Toxic cardiomyopathy: Alcohol, radiation, chemotherapy
High-output cardiomyopathy: tachycardia-induced cardiomyopathy (e.g., atrial fibrillation), thyrotoxicosis

for coronary artery disease, this would need to be ruled out first as the most common cause of HF. Mr. Smythe did have a cardiac PET scan performed, indicating a low probability of ischemia, and therefore the most likely culprit in this case would be hypertension that appears to be poorly controlled. He does, however, have a number of other risk factors that could have contributed.

Classification

What class of HF is Mr. Smythe?

Patients can be classified by both their symptoms and stage of disease (Table 14.7) [2]. Because Mr. Smythe has symptoms of HF and a reduced EF, he would be classified as Stage C. His functional class has been somewhat variable through the course of the last couple of months, starting at II then progressing to III–IV and now back to II–III. Functional class is typically variable and fluctuates as the course of disease fluctuates. It also tends to be somewhat subjective depending on the provider. However, regardless of its limitations, it is used clinically to give an overall description of functional capacity of patient with HF at baseline and from visit to visit (e.g., valuable for monitoring). Notably, this classification system has also been commonly used as entry criteria into clinical trials evaluating pharmacotherapy in HF.

Clinical pearls

When assessing functional capacity, first ascertain the types of activities a patient performs in their daily lives.

Do they do any regular exercise? Walking? Do they have stairs?
Do they do common housework? Vacuuming? Making beds? Carrying laundry?
Do they do any yardwork? Shoveling? Mowing the lawn? Gardening?

Often patients with HF have many comorbidities. Determine what their main limitation is when accounting for their functional capacity. For example, if a patient with HF and knee arthritis notes that they can only walk one block, ask them why they stop. Is it knee pain, or SOB, or both?

Prognosis

What is Mr. Smythe's prognosis?

Chronic HF typically has a poor prognosis, which is often worse than many cancers. On average, 50% of patients with HF will die within 5 years. If hospitalized, the in-hospital mortality rate is 4–7% [1]. The mode of death is typically pump failure or arrhythmia. The course of disease is usually progressive with increasing frequency of

Table 14.7 Classification systems used in HF [3]

ACC/AHA stages	New York Heart Association Functional Class (NYHA FC)
A: High risk for HF; No structural heart disease; No symptoms of HF	None
B: Structural heart disease; No symptoms of HF	I: No limitation in physical activity. Ordinary activity does not cause symptoms.
C: Structural heart disease; Symptoms of HF (prior or current)	I: See above
	II: Slight limitation in physical activity. Comfortable at rest. Ordinary physical activity results in symptoms.
	III: Marked limitation in physical activity. Comfortable at rest. Less than ordinary physical activity results in symptoms.
D: Refractory HF requiring specialized care	IV: Unable to carry in any physical activity without symptoms or symptoms at rest.

ACC/AHA American College of Cardiology/American Heart Association

acute events resulting in increased hospitalizations and mortality.

There are a number of risk stratification tools that can be used to identify patients at high risk; however, they are beyond the scope of this chapter.

Management

What are the goals of therapy for Mr. Smythe?

The goals of therapy when treating a patient with HF vary depending on the clinical situation. Priorities may also change depending on the whether the focus is on an acute exacerbation, chronic management, or end-stage disease and palliative care. Only a very small percentage of patients will receive ventricular assist devices or cardiac transplantation. The overall goals include the following:

- Decrease mortality
- Decrease morbidity
  - Decrease hospitalizations
  - Decrease HF exacerbations
  - Relieve/improve symptoms of HF
  - Improve functional capacity
  - Improve quality of life
- Manage risk factors that may cause or worsen HF

Given Mr. Smythe's current situation, all of these goals would be applicable.

How Should Mr. Smythe Be Managed?

The approach to treatment in HF involves both drug and non-drug measures as well as the consideration of whether the patient is in the acute or chronic phase of heart failure. Non-drug therapy includes sodium and fluid restriction, exercise, daily weights and device therapy (e.g., biventricular pacing, internal cardio-defibrillator).

Pharmacotherapy can be split into two categories, acute and chronic treatment. Acute treatment can include intravenous modalities such as inotropes and nitroglycerin; however, these treatments are outside the scope of this chapter. We will focus on the acute treatment of the ambulatory HF patient.

Acute Exacerbation of Heart Failure

An acute exacerbation of HF is typically characterized by worsening symptoms +/−congestion. Congestion is evaluated by doing an assessment of the patient's volume status which includes the following parameters: JVP, HJR, pulmonary percussion and auscultation, and examining the lower limbs for edema. Pharmacists can be taught to perform these physical examination skills. However, also being familiar with these findings when they are performed by others can help the pharmacist make decisions regarding drug therapy. Mr. Smythe has many signs and symptoms consistent with fluid overload (Table 14.8).

Typically, loop diuretics, most commonly furosemide, are the mainstay of treatment in patients that are fluid overloaded. Occasionally, loop diuretics may be combined with potent thiazides (e.g., metolazone) for additive effects and diuresis, especially in the case of diuretic resistance. This strategy is used sparingly due to frequent electrolyte abnormalities. The goal of therapy when using diuretics is to relieve congestion and improve symptoms. Starting dose (Table 14.9) will depend on patient symptoms, degree of volume overload, renal function, prior response to diuretics. Doses may need to be higher in cases of poor renal function. Diuretic dose should be reassessed often with a goal of the lowest effective dose or elimination of the agent completely if tolerated (and only using it as needed). Minimizing diuretic therapy will also support adding and up-titrating lifesaving medications.

Clinical Pearls

- Lower limb edema can be caused by a number of disease processes, including drugs (e.g., calcium channel blockers, NSAIDS, pregabalin, etc.). Remember to comprehensively assess the patient and put peripheral edema in context with other signs and symptoms of HF.
- Peripheral edema from an acute exacerbation of HF may take days or weeks to resolve and should never be used in isolation as the only marker of fluid overload. Consider all sign and symptoms when assessing fluid status and response to diuretics.

Table 14.8 Signs and symptoms consistent with congestion

Signs consistent with congestion	**Mr. Smythe**	**Case-specific examples**
Lung crackles/rale	Yes	crackles
Elevated jugular venous pressure (JVP); >4 cm above the sternal angle (ASA)	Yes	7 cm ASA
Positive hepato-jugular reflex (HJR)	Yes	
Peripheral edema	Yes	2+ pitting edema bilaterally to mid-shin ascites
S3 heart sounds	Yes	S3
Chest X-ray findings:		
pleural effusion pulmonary edema pulmonary venous redistribution	No Yes No	
Symptoms consistent with congestion	**Mr. Smythe**	**Case-specific examples**
Shortness of breath	Yes	Change from baseline activity: walking 8 block to 1 blocks climbing >2 flights of stairs to <1 flight new limitation doing yard work
Cough	Yes	Pre-existing cough but worse with orthopnea
Swelling (leg, abdomen)	Yes	Legs: Swelling in both of his legs, at times precluded wearing shoes. Abdomen: Poor appetite, even with hunger, feels full quickly and is unable to eat much (early satiety). Reports pants getting tighter and weight going up (~7 kg in 2 months) despite decrease intake and less activity. Weight loss post diuretic treatment (~3 kg)
Orthopnea	Yes	Reports sleeping poorly, SOB any time laid flat in bed. Sleeps with 2 pillows, down from 4/recliner
Paroxysmal nocturnal dyspnea (PND)	No	NA

Table 14.9 Common diuretics used in the treatment of HF

Drug	Starting dose	Maximum dose
Loop diuretics		
Furosemide	20–40 mg daily-BID	200 mg/day (caution with >120 mg)
Bumetanide	0.5–1 mg daily-BID	10 mg/day
Ethacrynic acid	25–50 mg daily-BID	400 mg/day (200 mg BID)
Thiazide diuretics		
Metolazone	2.5 mg daily	20 mg/day

BID twice daily

- Diuretics can often precipitate or worsen pre-existing gout. Be sure to assess if a patient has a history of gout and if they do, that they are on prophylactic medication (e.g., allopurinol)
- Sometimes other medications that lower blood pressure may require a dose reduction in order to adequately remove fluid using higher doses of diuretics. Just remember to minimize diuretics as tolerated post-acute exacerbation and restart/up-titrate required medications to doses prior to the event if possible.

Chronic heart failure

Chronic therapy can be started in the acute phase provided the patient is hemodynamically stable. The general approach to pharmacotherapy is outlined in Fig. 14.2 [3]. Pharmacotherapy is the cornerstone of HF management. Combination therapy is used in most patients to target either the negative or augment the positive neurohormonal effects (e.g., renin–angiotensin–aldosterone system, sympathetic nervous system, natriuretic peptide system) of a failing heart. Table 14.10 outlines the specific drug classes and parameters to consider when initiating and monitoring as part of

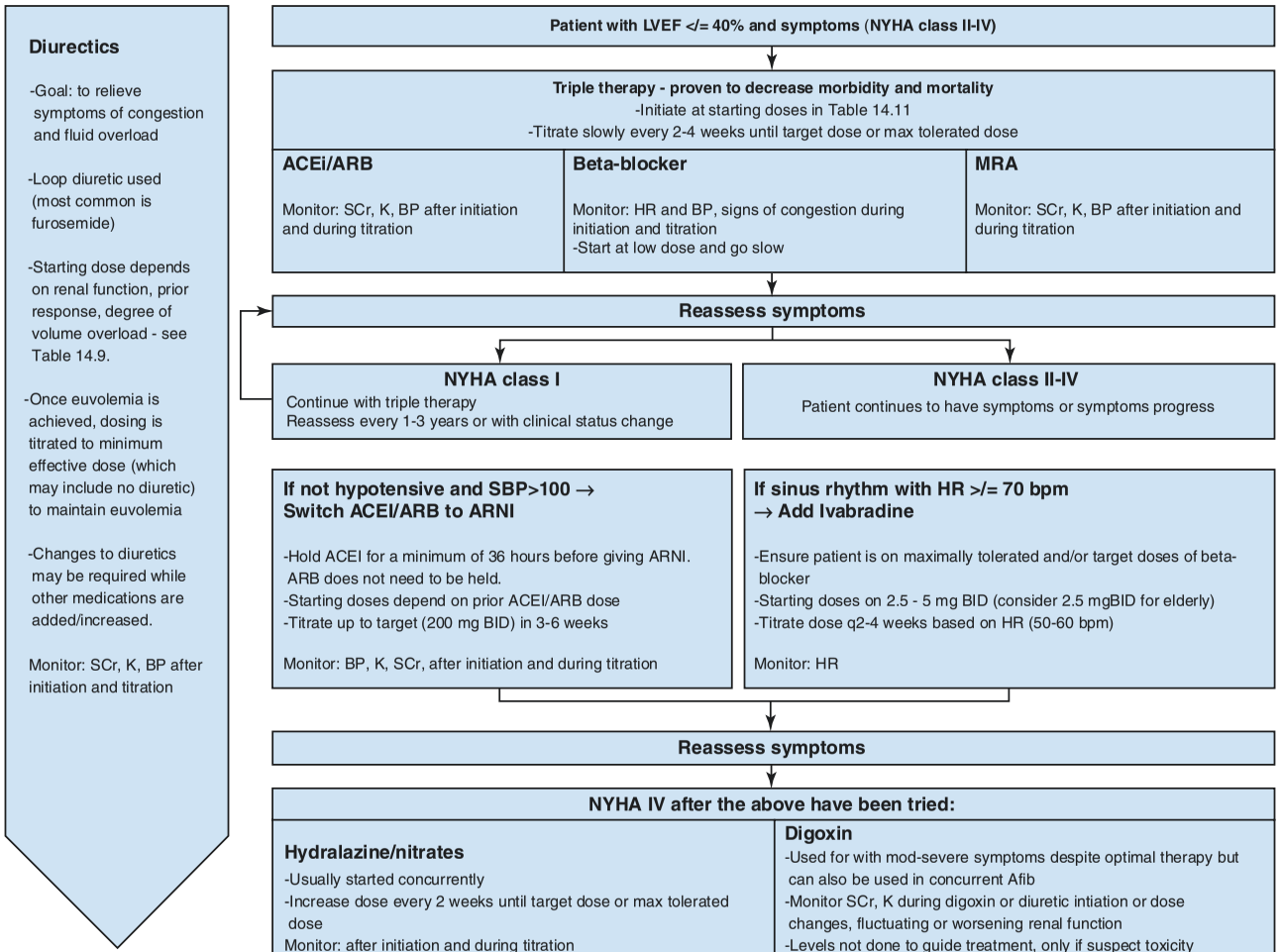


Fig. 14.2 Pharmacological approach to patients with HFrEF. (Adapted from the 2017 comprehensive update of the CCS guidelines for the management of heart failure [2]). Scr, serum creatinine; K, potassium; HR, heart rate; BP, blood pressure; SBP, systolic blood pressure

Table 14.10 Heart failure medications considerations for initiation and monitoring

Drug Class	Initiation	Monitoring
ACEI/ARB	***Labs:*** Establish baseline SCr and K+ Avoid in those with Scr > 220umol/L and K > 5.0 mmol/L ***Vitals:*** Establish baseline blood pressure Avoid in those with SBP < 100 mmHg ***Other:*** When starting an ACEi, document the presence or absence of cough prior to initiation Review other medications for drug interactions, including those that increase potassium and affect renal function	**Cough and angioedema:** Cough, characterized as dry and persistent, occurs in 10–20% of patients receiving ACE is and does not require discontinuation unless it is bothersome to the patient In patients with angioedema from an ACEi (uncommon <1%), an ARB can be used cautiously as there have also been reports of angioedema with ARBs **Renal function and electrolytes (K+):** Monitor SCr and K+ 1–2 weeks after initiation and dose increases Watch for trends in the K+: if continuously increasing or there is a significant change, pre-emptive adjustments may be required to prevent hyperkalemic (e.g., diet, other medications) Concurrent MRA therapy requires closer monitoring of K+ and Scr A change in Scr of up to 30% acceptable with introduction of ACEi/ARB. There is no immediate need to decrease the drug dose if the increase stabilized, but closer long-term monitoring should be considered **Blood pressure:** Exaggerated BP lowering may occur if starting at high doses or combined with diuretic therapy
B- blockers	***Vitals:*** Establish baseline heart rate and blood pressure Avoid if HR < 60 bpm or SBP < 100 mmHg Avoid if heart block ***Other:*** Should be started at very low doses and titrated slowly to prevent decompensation or worsening of HF initially In reactive airway disease, use a selective β-blocker cautiously (ex. bisoprolol or metoprolol) Reassess the need for other AV nodal blocking drugs used in combination (ex. digoxin, amiodarone)	**Heart rate and blood pressure:** Consider dose reduction if HR < 50 bpm If patient has low HR (HR 50–60) but is asymptomatic, there is no need to decrease dose **Fluid retention:** Transient fluid retention can occur when increasing β-blocker, and patient may require a diuretic dose change

(continued)

Table 14.10 (continued)

Drug Class	Initiation	Monitoring
MRA	***Labs:*** Establish baseline SCr and K+ Avoid in those with Scr > 220umol/L or GFR < 30 mL/min) and K > 5.0 mmol/L ***Vitals:*** Establish baseline blood pressure ***Other:*** Review other medications for drug interactions, including those that increase potassium and affect renal function	**Renal function and electrolytes:** Monitor K+ and SCr 2–3 days after initiation then 1 week after initiation. Check monthly × 3 months and then every 3 months thereafter. More frequent monitoring may be required in acute illness and those at high risk (DM, CKD, older) **Hormonal side effects:** Spironolactone may cause hormone-related side effects (e.g., gynecomastia (9%), impotence, post-menopausal bleeding) Eplerenone is a more selective mineralocorticoid receptor antagonist
ARNI (Sacubitril/ Valsartan)	***Labs:*** Establish baseline SCr and K+ Avoid in those with Scr > 220umol/L and K > 5.0 mmol/L ***Vitals:*** Establish baseline blood pressure Avoid in those with SBP < 100 mmHg ***Other:*** Review other medications for drug interactions, including those that increase potassium and affect renal function	**Side effects and tolerability similar to ACEI/ARB:** If patient has angioedema to ACEI or ARB, ARNI is contraindicated **Renal function and electrolytes:** Monitor SCr and K+ 1 week after initiation or dose increase, after dose stabilization, monitor every 3 months **Blood pressure:** ARNI can have more of a hypotensive effect compared to ACEI/ARBs
I_f inhibitor (Ivabradine)	***Vitals:*** Establish baseline heart rate Indicated in those with a HR > 70 bpm on maximally tolerated b-blocker therapy ***Other:*** Ivabradine works on the SA node, therefore, the patient must be in normal sinus rhythm	**Heart rate:** Target HR = 50–60 bpm Monitoring HR and adjusting the dose ivabradine every 2 weeks may be required.

Vasodilators (Hydralazine /nitrates)	Used if the patient is unable to tolerate ACEI/ARB/ARNI (significant worsening renal function or persistent hyperkalemia despite dose reductions of RAAS agent, elimination and modification of other contributing factors) ***Vitals:*** Establish a baseline heart rate	**Blood pressure** **Tolerance/administration:** Avoid continuous (24 hour) use of nitrates because patients can develop tolerance
Digoxin	**Labs:** Establish baseline SCr and K Dose may need to be adjusted based on renal function ***Vitals:*** Establish baseline heart rate	**Heart rate** **Electrolytes and kidney function:** Monitor K+ and SCr when changing digoxin dose, diuretic dose or dehydrating illness Increased monitoring may be required if the patient has decreasing or fluctuating renal function, elderly, or low body weight **Levels:** Digoxin levels are not done routinely and are not used to guide treatment. Levels are only done if one is suspecting toxicity
Diuretics	Diuretics are used to manage symptoms of fluid overload and congestion. ***Labs:*** Establish baseline SCr, sodium, and K ***Vitals:*** Establish baseline: blood pressure weight ***Other:*** Document if gout is present, consider prophylaxis	**Electrolytes and kidney function** Monitor SCr and electrolytes 2–3 days; then 1 week after initiation and dose changes Note renal function may also deteriorate with acute HF, so a fluid assessment is essential to assessing the cause of renal dysfunction **Blood pressure** Postural blood pressure (and heart rate) may help assess fluid status **Weight** Daily morning weight should be monitored in patients with HF with fluid retention or congestion that is not easily controlled with diuretics or in patients with significant renal dysfunction Monitor weight more closely in unstable or frail patients – rapid weight gain (1.5–2 kg) should prompt a rapid medical visit **Symptoms** Diuretics are titrated to symptom relief. When euvolemia is achieved, dosing is titrated to the minimum effective dose to maintain euvolemia, which may include no diuretic at all. Some patients may be managed with diuretic as needed and given parameters as to when the diuretic should be taken. (e.g. take 20 mg of furosemide when >1 kg gained in 3 days)

Table 14.11 Evidence-based drugs: start and target doses as shown in large clinical trials

Drug	Starting dose	Titration	Target dose
Angiotensin converting enzyme inhibitors (ACEi)			
Captopril	12.5 mg TID	Titrate every 2–4 weeks	25–50 mg TID
Enalapril	1.25–2.5 mg BID		10 mg BID
Lisinopril	2.5–5 mg daily		20–35 mg daily
Perindopril	2–4 mg daily		4–8 mg daily
Ramipril	1.25–2.5 mg BID		5 mg BID
Trandolapril	1–2 mg daily		4 mg daily
Angiotensin receptor blockers (ARB)			
Candesartan	4–8 mg daily	Titrate every 2–4 weeks	32 mg daily
Valsartan	40 mg BID		80 mg BID
Beta-blockers			
Carvedilol	3.125 mg BID	Titrate more slowly, every 4 weeks	25 mg BID 50 mg BID if >85 kg
Bisoprolol	1.25 mg daily		10 mg daily
Metoprolol*	6.25–12.5 mg BID		100 mg BID
Mineralocorticoid receptor antagonists (MRA)			
Spironolactone	12.5 mg daily	Titrate every 2–4 weeks	50 mg daily
Eplerenone	12.5–25 mg daily		50 mg daily
Angiotensin receptor blocker/neprilysin inhibitor (ARNI)			
Sacubitril/ valsartan	50–100 mg BID	Titrate every 3–6 weeks	200 mg BID
I_f inhibitor			
Ivabradine	2.5–5 mg BID	Titrate every 2 weeks	Target to heart rate 50–60 bpm Maximum dose: 7.5 mg BID
Vasodilators			
Isosorbide dinitrate	20 mg TID	Titrate every 2–4 weeks	40 mg TID Equivalent dose: NTG patch ≈ 0.8–1.0 mg/h Isosorbide-5-mononitrate ≈ 60 mg daily
Hydralazine	37.5 mg TID		75–100 mg TID-QID

the HF patient assessment. Both starting and target doses of these agents are listed in Table 14.11.

Physical Assessment Skills

Physical examination of the patient with HF will depend on the training of the individual pharmacist. All pharmacists should be able to perform blood pressure (supine, sitting and standing) and heart rate to assess pharmacotherapy in HF. Complete fluid assessment may be limited to advanced trained pharmacists. Most pharmacists should be able to assess for pitting edema in the lower extremities. Advanced trained pharmacists may also be able to do a focused pulmonary examination (assessing for pulmonary edema, pleural effusions, crackles and rales) and cardiovascular examination (extra heart sounds including S3, S4 and the JVP). Additionally, a focused gastrointestinal exam including an assessment for ascites, hepatomegaly, and the HJR may also be performed for complete fluid assessment as necessary.

Follow-Up Assessment

Follow-up is dictated by the patient's signs and symptoms and by any changes in medication. Follow-up should include an assessment of the patient's fluid status followed by review of their HF medications including assessment of adherence, target dose achievement and adverse effects (see Table 14.10). Adherence in the HF patient is complicated

by multiple co-morbidities and polypharmacy. Pharmacists are well-positioned to address and manage adherence issues in these patients. It has been shown that pharmacists can identify patients at risk and improve adherence in this population [4, 5].

Clinical Pearls

- Minimize pill burden where possible.
- If a patient experiences symptomatic hypotension, consider staggering doses of anti-hypertensives (e.g., am and pm dosing) and reassessing non-essential anti-hypertensives.
- Consider gout prophylaxis in patients on diuretics and prone to gout.
- Many patients may have lower urinary tract symptoms (e.g., incontinence, frequency, etc.). Discuss management of diuretic therapy to avoid non-adherence.

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Asthma

15

Kathleen Hayward and Sherif Hanafy Mahmoud

Chapter Objectives

1. Describe the epidemiology, risk factors, clinical presentation and diagnosis of asthma.
2. Describe the goals of therapy and management strategies for asthma.
3. Conduct an initial assessment of patients newly diagnosed with asthma.
4. Describe the role of inhaled medications and optimal inhalation device use in asthma management.
5. Conduct a follow-up assessment of patients with asthma.

Background

Asthma is a chronic variable disease of airflow obstruction which occurs across the age continuum, affecting over 8.4% of Canadians (2011 Survey on Living with a Chronic Disease in Canada). Asthma is characterized by variable airway obstruction attributed to airway inflammation and hyperresponsiveness and increased bronchial secretions [1]. Risk factors that have been identified to contribute to asthma development include heredity, personal and family history of allergies, high level of exposure to airborne allergens (pets, house dust mites, cockroaches and mould), frequent respiratory infections early in life and tobacco smoke exposure in utero or home environment.

Asthma control should be assessed regularly to guide adjustments to therapy. Many studies have shown that only about one-third of patients had their asthma controlled. Deaths due to asthma have occurred even in those thought to have mild asthma. The majority of these deaths occur outside the healthcare setting and involve people underestimating or delaying treatment for flare-ups, and this confirms the need for regular assessment. Pharmacists are uniquely positioned to provide care and ongoing assessment and monitoring to this population. They are the most accessible healthcare practitioners, and they are involved in dispensing the medications utilized for asthma management. The simple act of assessing inhaler technique of a patient at every opportunity, such as at prescription refills, can provide the chance for a conversation on control and identification of deterioration or risk. As a result, pharmacists can provide meaningful support to improve quality of life and decrease healthcare costs in patients living with asthma.

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Clinical Presentation and Diagnosis

Asthma should be diagnosed with a combination of history (symptoms and triggers), lung function testing (spirometry) and response to treatment. Asthma symptoms include cough, shortness of breath, a feeling of chest tightness and wheezing that can be episodic or persistent. Sudden onset of symptoms with physical activity or frequent longer-lasting upper respiratory tract infections might suggest asthma, and pharmacists can help identify those subjects and suggest referral to their physician for further assessment. Table 15.1 depicts a summary of asthma symptoms and possible exacerbating factors.

For asthma diagnosis, in addition to symptoms, lung function testing (spirometry) should show a minimum improvement of 12% and minimum of 200 ml increase in forced expiratory volume in 1 second (FEV1) after the administration of 400 mcg of inhaled salbutamol. Some people might not show reversible airway obstruction at the time of testing and may be referred to a specialist for further testing such as methacholine challenge test. A positive response to treatment (reversibility of airway obstruction following a bronchodilator) has been used in the past to diagnose asthma, but the objective lung function testing is the gold standard as it is now more readily available [1, 2]. Peak flow meters are not considered to be an acceptable method of diagnosis any longer according the Canadian Thoracic Society Asthma Guidelines [2].

There are a number of co-morbidities that mimic asthma symptoms and/or worsen actual asthma. These conditions should be identified to avoid misdiagnosis and unnecessary treatments. Examples of these comorbidities include rhinosinusitis, gastroesophageal reflux disease (GERD), vocal cord dysfunction, heart failure, pulmonary hypertension, chronic obstructive pulmonary disease (COPD) and cystic fibrosis [1].

Table 15.1 Symptoms and possible exacerbating factors of asthma

Symptoms	Aggravating factors
Cough Shortness of breath (SOB) Feeling of chest tightness Wheezing (a high-pitched sound secondary to airway narrowing)	Allergens, e.g. animal dander, pollens, rats, cockroaches Smoke, e.g. cigarette smoke Respiratory tract infections (viral and bacterial) Sinusitis Physical exertion Cold weather Occupational exposure to certain chemicals Some drugs such as non-selective beta blockers

Management

The goals of asthma management are to control the symptoms and prevent or minimize future risk of short- and long-term complications, morbidity and mortality. This is in addition to avoiding adverse effects of medications. Asthma management guidelines are available and detailed from the Canadian Thoracic Society (CTS) [2] and the Global Initiative for asthma (GINA) [3]. Asthma management includes both non-pharmacological and pharmacological modalities to achieve treatment success. *Non-pharmacological management* of asthma involves avoiding environmental triggers such as animals, pollens, infections, moulds, cigarettes or forest fire smoke, occupational chemicals or strong fragrances. Some triggers are difficult to avoid, and allergy testing by an allergist, respirologist or otolaryngologist may be needed to find out what triggers patient's asthma. In addition, the continuum includes confirming the diagnosis, patient education and provision of a written action plan (individualized management plan). An asthma action plan allows the patient to monitor for symptoms worsening, list triggers and record the frequency of using relievers such as short-acting beta 2 agonists. In addition, it provides directions for self-management and referral. Figure 15.1 provides a summary of the asthma management continuum for children older than 6 years and adults [2].

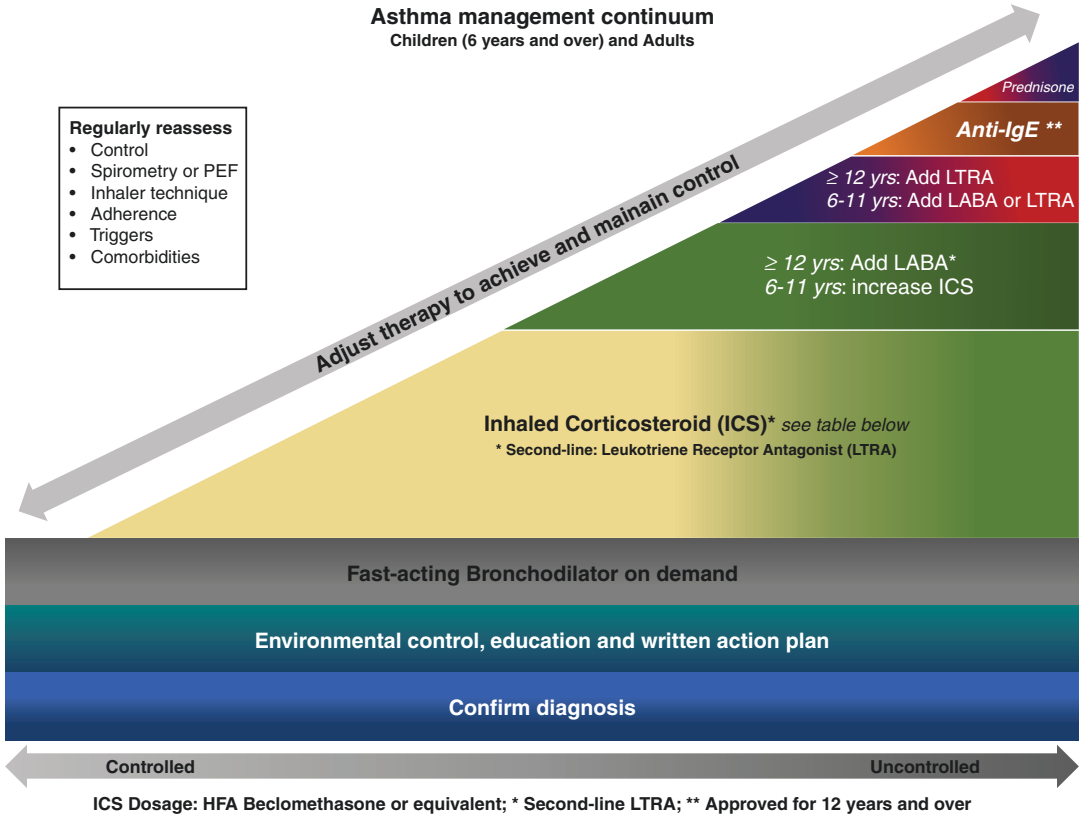


Fig. 15.1 Asthma management continuum. IgE, Immunoglobulin E; PEF, Peak expiratory flow; yrs., Years. (Adapted from Lougheed et al. [2] under the Creative Commons Attribution License)

Pharmacological Options for Asthma

Asthma pharmacotherapy is generally divided into two main classes: symptomatic therapy (*symptom relievers*) and maintenance therapy (*controllers*). Relievers are used, when needed, for a quick relief of asthma symptoms, and they are available as inhaled formulations. All patients should have a reliever prescribed in addition to their maintenance therapy regardless of their asthma severity. On the other hand, controllers are used regularly to prevent worsening of asthma and progression of airway remodelling. Controllers are generally inhaled, but there are other options that could be oral (e.g. leukotriene receptor antagonists) or injectable (e.g. biologics). Table 15.2 summarizes asthma treatment options available in Canada. Table 15.3 depicts the comparative dosing categories of inhaled corticosteroids [4].

Initial and ongoing asthma management decisions depend on the patient's asthma severity (specialist assessment is required) [1–3]:

- Patients with very mild asthma with intermittent symptoms can be managed with short-acting beta-2 agonists (SABA) when needed.
- Individuals presenting with mild asthma symptoms should be initiated on low-dose inhaled corticosteroids (ICS) as a controller. Leukotriene receptor antagonists (LTRA) could be provided as a second-line option for patients who are unable or refuse to take ICS.
- If asthma symptoms are not controlled on a low-dose ICS, options will include a medium-dose ICS or a low-dose ICS combined with a long-acting beta 2 agonist (LABA). It is important to note that LABA should only be used with an ICS as LABA alone has been

Table 15.2 Asthma treatment options available in Canada

Category	Class	Drug name	Comments
Relievers	Short-acting beta 2 agonists (SABA)	Salbutamol	Available: pMDI, Diskus, oral inhalation solution Drug of first choice as reliever therapy; used prn Use of valved holding chamber (VHC) improves deposition especially if symptoms are present
		Terbutaline	Available: DPI
	Short-acting muscarinic antagonists (SAMA)	Ipratropium	Available: pMDI; oral inhalation solution Alternative reliever in patients experiencing adverse effects from SABA (tremors, tachycardia) - Rarely used as a reliever
Controllers (inhaled)	Inhaled corticosteroids (ICS)	Beclomethasone	Cornerstone of asthma controller therapy Available in multiple formulations: pMDI, DPI and oral inhalation solution (budesonide)
		Budesonide	
		Ciclesonide	
		Fluticasone furoate	
		Fluticasone propionate	
		Mometasone	
	Long-acting beta2 agonists (LABA)	Formoterol	They should not be used without concurrent ICS
		Salmeterol	
	ICS/LABA combination	Budesonide/formoterol	Budesonide/formoterol can be used as both controller and reliever Available: DPI, pMDI, Diskus
		Fluticasone furoate/vilanterol	
		Fluticasone propionate/ salmeterol	
		Mometasone/ formoterol	
	Long-acting muscarinic antagonists (LAMA)	Tiotropium in SMI	SMI is approved for asthma It could be considered as an add-on therapy in patients on ICS/LABA
Controllers (oral)	Leukotriene receptor antagonists (LTRA)	Montelukast	Second-line to ICS It could be used in combination with ICS
	Methyl xanthines	Theophylline	Limited use due to adverse effects
Others	Oral corticosteroids (OC)	Prednisone	Taken for short period of time in case of acute exacerbations
Biologics (injectables)	IgE antibody	Omalizumab	It could be considered for patients with severe uncontrolled asthma and have allergies Subcutaneous injection every 2–4 weeks
	IL-5 inhibitor	Mepolizumab/ Benralizumab	Subcutaneous injections For uncontrolled asthma with eosinophilia
		Reslizumab	Intravenous infusion every 4 weeks Add-on for uncontrolled asthma with eosinophilia

DPI dry powder inhaler, *pMDI* pressurized metered dose inhaler, *prn* when necessary, *SMI* soft mist inhaler

associated with increased mortality risk in patients with asthma [4, 5].

- If symptoms are not adequately controlled, the next step will include a medium-dose ICS + LABA, or LTRA + low- or medium-dose ICS.
- Patients with severe or uncontrolled asthma could benefit from high-dose ICS + LABA.

Table 15.3 Comparative dosing categories of inhaled corticosteroids [4]

	ICS daily dose in mcg					
	Paediatric (6–11 years)			Adults and adolescents (≥ 12 years)		
ICS name	Low	Medium	High	Low	Medium	High
Beclomethasone	≤200	201–400[a]	>400[a]	≤ 250	251–500	>500
Budesonide	≤400	401–800	>800	≤400	401–800	>800
Ciclesonide	≤200	201–400[a]	>400[a]	≤200	201–400	>400
Fluticasone furoate	N/A	N/A	N/A	100		200
Fluticasone propionate	≤200	201–400	>400[a]	≤ 250	251–500	>500
Mometasone	100	≥200–<400	≥400	100–200	>200–400	>400

ICS inhaled corticosteroids
[a]These doses are not approved for use in children in Canada

Initial Assessment of a Patient Newly Diagnosed with Asthma

Pharmacists play an important role in the management of patients with asthma. They are able to assess the patients for the presence of any potential drug-related problems including patients' understanding of their medications and proper inhaler techniques. Similar to other medical conditions, proper initial assessment of patients newly diagnosed with asthma requires collection of a complete relevant history (demographics, history of present illness, medical history, social history, medications, adherence concerns and physical examination findings). In addition, initial assessment includes the following:

- *Identification of the risk factors for poor asthma control:* While gathering a patient history, pharmacists can assess the presence of any modifiable risk factors that can affect proper control of the patient's asthma (Table 15.4). Presence of any of the risk factors might result in an increased risk of exacerbations even in patients with few asthma symptoms [3]. Pharmacists can help addressing any of the modifiable risks with the patient through an individualized asthma management plan. This involves avoiding triggers, making sure the patient will be adherent to drug therapy and administering inhalers using the correct technique (discussed later).

Table 15.4 Risk factors associated with poor asthma outcomes [3]

Risk category	Description
Risk factors of asthma exacerbations[a]	Uncontrolled asthma (see "Follow-up Assessment" section) Exposure to allergens or tobacco smoke Frequent use of relievers (use of more than one 200-dose canister per month is associated with increased mortality risk) Presence of risk factors of poor adherence to therapy (see Chap. 2 for more information about adherence) No ICS prescribed Incorrect inhaler technique Low FEV1 (particularly if less than 60% predicted) Obesity Rhinosinusitis Pregnancy Presence of food allergies Major psychological and socioeconomic issues Eosinophilia in sputum and/or blood One or more exacerbations in the last year ICU admission due to asthma
Risk factors for fixed airway limitations	No ICS prescribed Exposure to tobacco smoke or noxious chemicals Low initial FEV1 Chronic excessive mucus secretion Eosinophilia in sputum and/or blood
Risk factors for medication-adverse effects	Frequent use of systemic corticosteroids Use of potent and/or high-dose ICS Incorrect inhaler technique

FEV1 forced expiratory volume in 1 second, *ICS* inhaled corticosteroid
[a]Presence of any of these risk factors increases the risk of exacerbations even in patients with few asthma symptoms

- *Appropriateness of asthma pharmacotherapy given patient's asthma severity:* As discussed in the "Management" section, initial and ongoing asthma management decisions depends on the patient's asthma severity. For example, initial asthma management could be more intensified (e.g. high-dose ICS) if the patient presents with more severe symptoms. On the other hand, patients with mild asthma should benefit from low-dose ICS as a controller + SABA as a reliever.
- *Appropriateness of asthma pharmacotherapy given patient's demographics:* Management recommendations vary among different age groups (see Fig. 15.1). We refer the readers to asthma guidelines for more details about age-specific recommendations [2–4]. Pharmacists need to make sure that patients are getting the appropriate ICS dose (see Table 15.3).
- *Presence of asthma action plan:* Asthma action plan is a written individualized management plan that contains instructions for the patient regarding adjusting reliever and controller therapies according to the patient's symptoms. It allows the patient to monitor for symptoms worsening, list triggers and record the frequency of using relievers such as short-acting beta 2 agonists. In addition, it provides directions for red flag symptoms that prompt referral to the emergency department. Figure 15.2 depicts an example of an asthma action plan.

Asthma Self-Management Education and Correct Inhaler Technique

The need for self-management education is a place where pharmacists can have a great impact by optimizing inhaler technique and counselling patients on when to use their asthma medications. One of the most important factors contributing to asthma treatment success is inhaler administration using the correct technique. Wrong inhaler technique might result in treatment failure secondary to suboptimal delivery of the drug or adverse reactions secondary to incorrect administration instructions. Table 15.5 depicts the common steps for using inhalers. The pharmacist toolkit for assessing and teaching inhaler technique should contain:

- Placebo devices that are used to demonstrate the correct technique with or without a valved holding chamber
- Device instruction sheets in languages that are used in the pharmacist's practice
- A Peak Flow Meter sample for demonstration (used for monitoring not diagnosis)
- Sizing chart for mask sizes for chambers, if needed
- Copies of patient education booklets, sheets, airway pictures, list of applications for recording medications and/or symptoms

The following are examples of resources and tools used for asthma teaching:

- "I Can Control Asthma" website: It contains helpful resources such as asthma education pamphlet that is available in 13 different languages, paediatric asthma action plan and instructional videos. Website address: https://www.ucalgary.ca/icancontrolasthma/.
- The Lung Association: If people have difficulty learning to use devices, there are videos on proper inhaler technique available in this website. Web address: https://sk.lung.ca/lung-diseases/inhalers.
- Manufacturers often have good patient education videos or printed device instruction sheets, sometimes in multiple languages.
- Asthma Canada (www.asthmameds.ca).

It is important to counsel patients that there are often videos available in the internet that might show incorrect inhaler techniques. Only use resources from a reliable organization website.

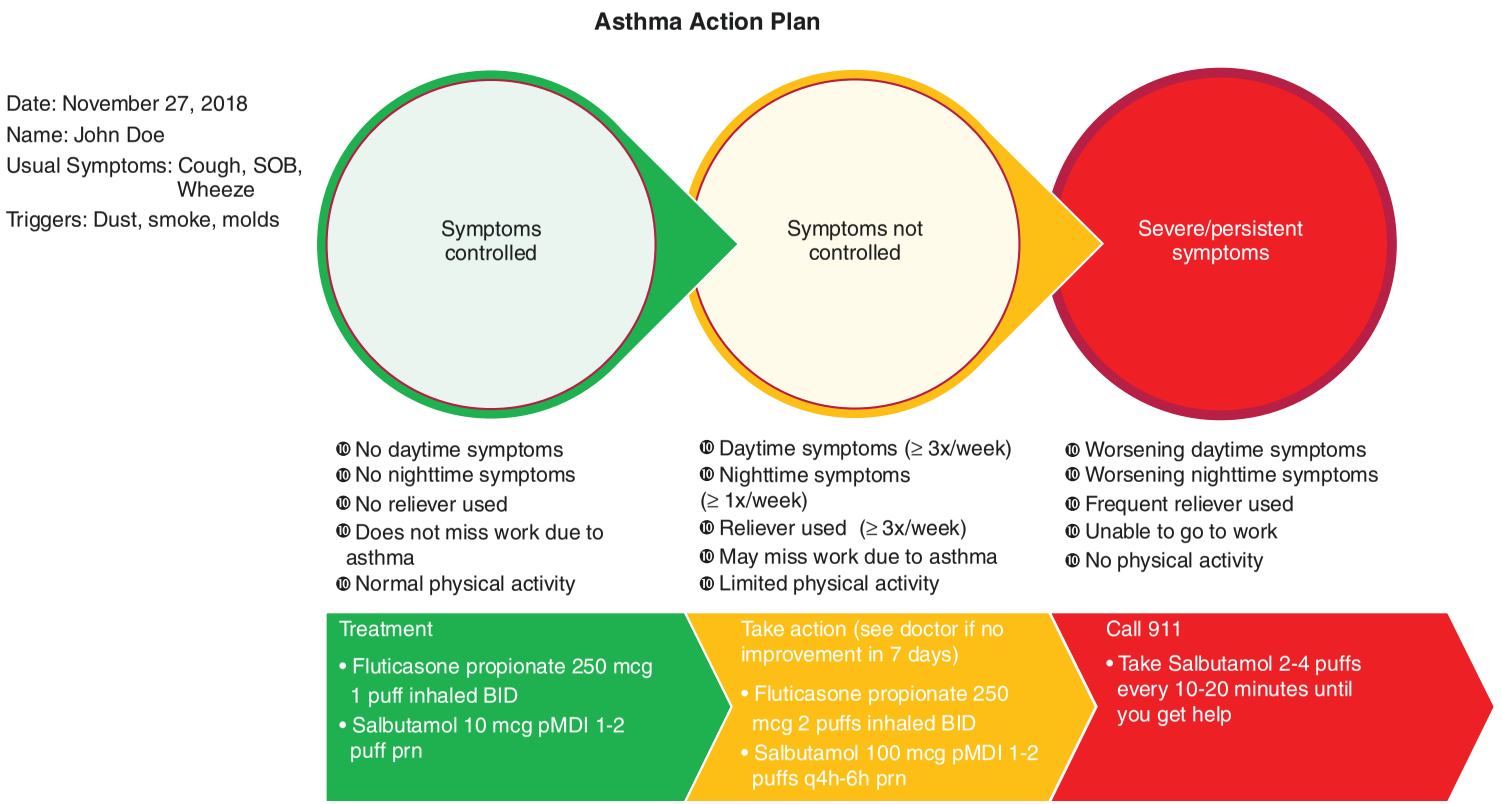


Fig. 15.2 An example of asthma action plan. BID, twice daily; pMDI, pressurized metered dose inhaler; SOB, shortness of breath

Table 15.5 Common steps for using inhalers[a]

1. Remove cap or cover from the inhaler
2. Shake or load dose, if needed; attach chamber, if needed. Priming for new or not recently used devices is detailed in the patient's package handout (usually 2–4 sprays with pMDI)
3. Exhale away from inhaler, place mouth on mouthpiece of the device or chamber
4. Discharge a single dose and inhale fully into lungs, not just mouth (slowly or quickly depending on device). Do not swallow
5. Hold breath for up to 10 seconds as specified by the manufacturer (six tidal breaths may be used with pMDI and two-way-valved holding chamber)
6. Exhale away from the device
7. Wait to catch breath and prepare the next dose, if needed.

[a]It is important to be familiar with variations in steps for all devices, and these are best learned through the manufacturer's patient package inserts, single page device sheets or videos from reliable sources such as the Lung Association or Asthma Society. Use caution if using resources that are not validated by these organizations or your regional health authority. Some videos on YouTube use alternate incorrect steps even though they are supposedly from healthcare providers

Follow-Up Assessment

Follow-up assessments of patients with asthma is essential to maintain disease control given its variable nature and propensity to be aggravated by a myriad of factors (see Table 15.1). Patient progress regarding asthma management can be more easily implemented with regular assessments. Travel, new employment, renovations at home or work and addition of new respiratory irritants such as inhaling cannabis, electronic vaporizer fumes can present risk for poor asthma control. Every refill for an asthma medication should trigger a brief follow-up. This could be flagged in the pharmacy refill system so that the pharmacist is reminded for follow-up.

Adherence

Adherence to controller therapies and triggers avoidance is very important for proper asthma control. Pharmacists play an important role in helping patients achieve optimal adherence. They should check with their patients if they are taking their therapies as directed and work on enforcing compliance. In addition, pharmacists have an advantage in being able to check adherence with medications prescribed through examining the patient's prescription fill records. Barriers to nonadherence in other illnesses also apply to asthma. See Chap. 2 for more details about medication adherence. In addition, some patients often tend to stop their medications when they have no symptoms. Patients should be counselled to continue taking their controller therapies even if their symptoms are under control. An asthma action plan will be very helpful in promoting adherence.

Control

CTS Asthma Guidelines recommend asthma control should be assessed at every contact with the patient [2]. Improvement in asthma symptoms should be seen within days from controllers initiation with full benefit expected within 3–4 months [3]. CTS outlined the criteria for asthma control (Table 15.6) [2]. Deviation from these control criteria (e.g. daytime symptoms more than 3 days per week or absence from

Table 15.6 Asthma control criteria[a]

Characteristics	Frequency or Value
Daytime symptoms	Less than 4 days per week
Night-time symptoms	Less than one night per week
Physical activity	Normal
Exacerbations	Mild; infrequent
Absence from work or school due to asthma	None
Need for fast-acting reliever	Less than 4 doses per week
FEV1 or PEF	More than or equal 90% personal best
PEF diurnal variation[b]	<10–15%

FEV1 forced expiratory volume in 1 second

[a]Reprinted under the Creative Commons Attribution License. From Lougheed et al. [2]

[b]Diurnal variation is calculated as the highest peak expiratory flow (PEF) minus the lowest PEF divided by the highest PEF multiplied by 100 for morning and night (determined over a 2-week period)

work due to asthma) suggests loss of control and increased risk of future exacerbations. Examples of questions to be asked:

- *Do you have cough, wheeze, tight chest or shortness of breath three or more times in the last week?*
- *Do you have night-time symptoms?*
- *Is physical activity, work or exercise, interrupted by your symptoms?*
- *Do you use your reliever inhaler more than three times weekly?*
- *Have you missed work or school due to asthma symptoms?*

Control is achieved if patient is able to answer "No" to the five questions listed above. Asthma control could also be assessed using any of the validated patient questionnaires such as Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ). In addition, occurrence of two or more severe exacerbations requiring oral corticosteroids or one or more serious exacerbations requiring hospitalization in the previous year or FEV1 less than 80% of personal best following a reliever are also considered uncontrolled asthma [4]. Signs and symptoms of acute asthma exacerbation include difficulty breathing, increased respiratory rate, cyanosis and pulsus paradoxus (systolic blood pressure reduction during inspiration) [1].

Pharmacists should be watching for uncontrolled asthma, which is a risk for future exacerbations. Not all pharmacists will have access to this information and must rely on patient reported events; however, efficient monitoring strategies could be attained through collaboration with family physicians or specialists. For example, a number of physicians believe that when they prescribe medications, the prescriptions will be filled; however, as pharmacists know, this does not always happen.

Lack of symptom control suggests the need for intensification of asthma pharmacotherapy. However, before intensifying asthma management in patients presenting with poorly controlled disease, an assessment of potential factors of therapy failure should be conducted. These factors include confirming asthma diagnosis, correct inhaler techniques, comorbidities, inability to afford medication, lack of understanding of the role of controller medications and relievers, adherence to pharmacotherapy and triggers avoidance. Exceeding doses of short-acting bronchodilators can be a sign of uncontrolled asthma or exacerbation requiring management in a facility with advanced treatment options (e.g. oxygen, non-invasive ventilation). Reliever overuse could be a red flag that prompts referral to the patient's physician. Respiratory specialists are generally very happy to receive communication from community pharmacists to ensure that patients are able to follow the plan they agreed to. If no Asthma Action Plan has been provided, the pharmacist can suggest one or fill out based on the treatment that controlled patient's asthma previously. If the patient has never achieved control, an escalation in therapy or referral may be warranted. Below is an example of pharmacist's communication regarding a patient with uncontrolled asthma due to non-adherence to an ICS.

Dear Dr. Jones,

On November 30th, I assessed Joanne Brown's asthma as she had come in to obtain another salbutamol 100mcg MDI for her shortness of breath. She has not filled her fluticasone propionate/salmeterol 250/50 mcg Diskus in the last 6 months. She discontinued it as it made her lose her voice, which impacted her work.

I have reviewed her technique and suggested a change to an MDI with valved holding chamber. Fluticasone propionate/salmeterol 125/25 two puffs every 12 hours via spacer would be a good choice to avoid this side effect. Please contact me with questions or comments.

Please provide a prescription for this routine. I will follow up with her in two weeks to check if her asthma control has improved. I can fill out an action plan if you wish and/or ask her to follow up with you.

Community pharmacist, Joe

Peak Flow Meter

In asthma, many patients use a peak flow meter, which assesses how quickly they can exhale. Patients should know what their peak expiratory flow (PEF) is when they are not experiencing any symptoms, as a decrease can show a worsening in asthma control. From a pharmacy perspective, patients who have asthma and use a peak flow meter could have their normal value recorded while completing a care plan in order to monitor disease progression. PEF more than or equal 90% personal best is one of the indicators of asthma control [2]. Readings from 90–60% (in conjucntion with symptoms assessment) may suggest the need to escalate therapy. Not everyone requires a PEF meter as they cost and require monitoring and recording. Specialists often do not suggest them as they find patients do not use them.

Adverse Reactions

Pharmacists play an important role in monitoring how patients tolerate asthma drug therapy as this can be a common barrier for non-adherence. Oral thrush is a potential adverse reaction of ICS. Oral thrush can occur in asthma patients especially if they do not rinse, gargle and spit out water after administering the medication. ICS can also cause hoarse voice. If the rinses do not help changing to other devices, for example, an MDI with a chamber, it could greatly reduce this adverse effect. In addition, some people experience coughing or throat irritation when taking dry powder inhalers. Adjusting the force of their inhalation can reduce this problem. This will require assistance from the pharmacist to demonstrate and observe the changes made by the individual. This is where having placebo devices are crucial. Table 15.7 summarizes some adverse reactions of asthma pharmacotherapy.

Table 15.7 Adverse reactions of asthma pharmacotherapy[a]

Drug Class	Possible Adverse Effects
Short-acting beta 2 agonists (SABA)	Tremors, tachycardia, palpitation, nervousness, headache
Short-acting muscarinic antagonists (SAMA)	Dry mouth, metallic taste, upper respiratory tract infection (URTI)
Inhaled corticosteroids (ICS)	Oral thrush, hoarse voice, dysphonia, sore mouth, URTI
Leukotriene receptor antagonists (LTRA)	Headache, abdominal pain
Long-acting beta 2 agonists (LABA)	Headache, pharyngitis
Long-acting muscarinic antagonists (LAMA)	Dry mouth, metallic taste, URTI, headache
Systemic corticosteroids	Taking frequent courses of oral corticosteroid can lead to many adverse effects such as osteoporosis, cataracts, gastric ulcers, sleep difficulties, weight gain, hyperglycemia, increased complications from respiratory infections.

[a]This list is not comprehensive; consult individual drug monographs for a complete list of possible adverse effects

Complications

Impact on Daily Life

Asthma can impact daily life in an insidious manner which limits ability to stay fit and healthy. Asthma can interrupt school or work attendance and diminish exercise tolerance. Children with asthma can become socially isolated. For example, they may not be picked up for team sports or attending social activities. In addition, presence of night-time symptoms might affect their sleep.

Severe Asthma

Severe asthma represents approximately 5–10% of asthmatic patients. Severe asthma is defined by CTS as "Asthma which requires treatment with high-dose ICS, as outlined in Table 15.3, and a second controller for the previous year, or systemic corticosteroids for 50% of the previous year to prevent it from becoming "uncontrolled", or which remains "uncontrolled" despite this therapy" [4]. Patients with severe asthma require assessment by a specialist and might need esca-

lation of therapy such as the use of high-dose ICS/LABA combination with or without LAMA, LTRA or theophylline. Biologics could also be utilized. Note that presence of severe asthma does not usually mean that the asthma is uncontrolled (discussed under "Control").

Prevention

Pharmacists can counsel patients on how to avoid triggers as they do follow-up assessments throughout the year. Recommendations to investigate environmental triggers could result in changes to the patients' own homes – such as adding dehumidifiers or air conditioners and removal of wood/coal burning heat sources, tobacco or cannabis smoke and animals. Being aware of pollen counts, outdoor air quality through the Air Quality Health Index (AQHI) app or website, (https://www.canada.ca/en/environment-climate-change/services/air-quality-health-index.html) which can be personalized for the local area – could be very helpful. Influenza vaccination is recommended annually in patients with asthma with a few exceptions in patients with severe asthma or recent or current wheezing. This because asthmatics are at high risk for influenza-related complications. The National Advisory Committee on Immunization (NACI) recommends that asthma control should be optimized prior to any vaccination. In addition, some patients may be on chronic oral corticosteroids and this might affect eligibility for vaccination. Generally, a person who is on less than 20 mg of prednisone for less than 1 month may receive any inactive immunization. Pharmacists need to consult the policies for their health authority and manufacturer's recommendations with regard to vaccination eligibility.

Smoking cessation and/or avoiding second-hand smoke can be very useful in improving asthma control. Pharmacists not only can provide behavioural support and suggestions/prescriptions for medications, but also they can refer patients and families to other existing resources such as provincial or national Quit programs or Help Lines, national associations such as the Lung Association and Employee and Family Assistance programs.

Clinical Pearls

- Pharmacists play an important role in the management of patients with asthma.
- Avoiding triggers is very important contributor to treatment success.
- Assessment at follow-up visits (refills) includes review of inhaler technique and use, evaluation of how well the therapy is managing the patient's symptoms and improving quality of life, frequency of exacerbations and adverse effects.
- Ensure each asthma patient has an Action Plan and knows what to do in case of lack of symptom control.

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Chronic Obstructive Pulmonary Disease

16

Renette Bertholet and Inessa McIntyre

Chapter Objectives

1. Describe the epidemiology, pathophysiology and management of chronic obstructive pulmonary disease (COPD).
2. Assess patients with COPD.
3. Identify the red flags in patients presenting with COPD that prompt referral to healthcare practitioners or the emergency department.

Background

Chronic obstructive pulmonary disease (COPD) is "a *treatable* and *preventable* disease characterized by *progressive airflow limitation* (obstruction) that is *not fully reversible* and is associated with an *abnormal inflammatory response* of the lungs to noxious particles or gas" [1]. Pharmacists play an important role in identifying patients that are at risk for COPD, referring for diagnosis and managing drug therapy. Pharmacists assess drug effectiveness and safety but also assess for adherence and proper use of inhalers, which are a mainstay of COPD pharmacotherapy. In collaboration with other healthcare professionals, pharmacists can improve quality of life for patients with this progressive disease and ensure each COPD patient has an action plan and knows what to do in case of an exacerbation.

Epidemiology

COPD is the fourth leading cause of death in Canada [2]. COPD is generally underdiagnosed in Canada. To illustrate, while about 4% of Canadians between 35 and 79 years of age self-report a COPD diagnosis [2], the prevalence of COPD among randomly sampled residents in Vancouver aged 40 or older has been estimated to be 19% (BOLD study) [3]. Additionally, the Canadian Health Measures Survey conducted between March 2007 and February 2008 found that 17% of Canadians aged 35–79 had airflow obstruction compatible with COPD [3]. Conversely, concern surrounds the overdiagnosis of COPD in patients as well, as 60–70% of Canadians between 35 and 79 who reported being diagnosed with COPD did not meet the diagnostic spirometry criteria [3]. Given the potential for over and underdiagnosis of this condition, it is important for pharmacists to be on alert to help identify and refer patients for timely and appropriate diagnosis.

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Risk Factors and Pathophysiology

As COPD is a treatable and preventable disease, early identification of at-risk patients and addressing underlying causes and risk factors to limit disease progression are important roles of the pharmacist. Risk factors for COPD can be *environmental* or *intrinsic*. Environmental factors include cigarette smoking (most common), occupational exposure (e.g., dust, chemicals), and air pollution. Intrinsic host factors include alpha-1-antitrypsin (AAT) deficiency, a rare inherited disorder of airway hyper-responsiveness and impaired lung growth [1].

Inhalation of noxious particles and gas results in an abnormal inflammatory response leading to destructive changes in the airways. The culprit noxious substance in 85–95% of COPD cases is cigarette smoke. It causes inflammation and subsequent cell damage through a number of different mechanisms that are distinct from those seen in asthma. In COPD, neutrophils, macrophages, and CD8 lymphocytes are activated, releasing a variety of inflammatory mediators. This results in lung damage and ciliary destruction, impairing ciliary motility and the ability to expel mucus. Additionally, goblet cell production is stimulated, leading to an increase in mucus production. The result is a vicious cycle of chronic inflammation and mucus production. Small airways (respiratory bronchioles) may become clogged with mucus or distorted by fibrosis. Furthermore, inflammatory cells release proteases that dissolve proteins in the alveolar walls, thereby causing loss of alveolar attachments and loss of elastic recoil. This results in diffuse airway narrowing, plugging with mucus, loss of elastic recoil, air trapping, and lung hyperinflation. Over time, as the disease progresses, there will be inequalities of ventilation/perfusion, destruction of vascular beds, hypoxemia, and carbon dioxide retention [1].

COPD has previously been sub-categorized into "chronic bronchitis" and "emphysema." Cough, chronic inflammation, loss of cilia, and mucus production are associated with chronic bronchitis. Destruction of alveoli and loss of elastic recoil are associated with emphysema. It is now recognized that most patients with COPD have elements of both. An example of an exception is AAT deficiency, which is typically emphysematous [1]. COPD patients typically present with a chronic cough, sputum production, and shortness of breath that progresses and persists over time. Spirometry, which measures airflow limitation, is required for diagnosis [1]. Not all patients with chronic cough have COPD. When assessing a patient with chronic cough, there are other conditions that should be ruled out. These include asthma, lung cancer, tuberculosis, left heart failure, interstitial lung disease, cystic fibrosis, idiopathic cough, chronic allergies, postnasal drip syndrome, upper airway cough syndrome, gastroesophageal reflux, and medication-induced cough [4].

Initial Assessment of a Patient with Chronic Cough

PK is a 52-year-old female patient presenting to your pharmacy or clinic requesting something for her chronic cough. What initial assessments might contribute to the diagnosis of COPD?

Screening

Screening for COPD and possible referral to primary care providers for diagnosis is an important step in assessing patients presenting with chronic cough. The following questions are helpful in screening patients [2]:

1. Are you 40 years of age or older?
2. Are you a current or former smoker?
3. Do you have a history of occupational exposure to dusts and chemicals?
4. Do you cough regularly?
5. Do you cough up phlegm regularly?
6. Do simple chores make you short of breath?
7. Do you wheeze when you exert yourself or at night?
8. Do you get frequent colds that persist longer than those of other people you know?

Patients who are 40 years or older, with a history of smoking or exposure to dusts or chemicals, AND answered YES to any of questions 4–8 above should be referred for further assessment.

Patient History

Additional targeted questions that are valuable in the assessment of COPD include the following:

- *Social history*: exposure to environmental or occupational risk factors such as smoking
- *Family history*: family history of COPD or other respiratory diseases, e.g., history of AAT deficiency.
- *Past medical history*: history of exacerbations or hospitalizations for respiratory disorders in the last 12 months. It is also important to keep in mind that COPD is associated with a number of comorbid conditions such as ischemic heart disease, anemia, cachexia, osteoporosis, depression, anxiety, and cancer to name a few [1, 2].
- *Symptoms*: In addition to the symptoms described in the initial screening questions above, the patient may also experience difficulty sleeping. This may be due to awakening resulting from episodes of coughing and shortness of breath or sleep apnea. It may also be related to anxiety or depression, which is a common comorbidity in patients with COPD. The patient may also report a loss of energy or fatigue. This may be due to the extra work it takes to breathe, poor oxygen exchange in the lungs, and/or polycythemia. Furthermore, assessment of symptom severity is important (see below).
- *Red flag symptoms* that require immediate referral include excessive shortness of breath, chest pain, blood in sputum, and change in mental status (e.g., confused and/or drowsy).

Physical Assessment

In addition to targeted questions, depending on the clinical setting, the pharmacists might utilize the following physical assessment skills.

Inspection

Pharmacists can observe any of the following findings consistent with COPD:

- Barrel chest
- Accessory muscle use
- Pursed lip breathing
- Prolonged expiration
- Cyanosis (bluish discoloration of the skin and lips)
- Tachypnea (respiratory rate > 20 breaths per minute)
- Signs of being a smoker: smell of nicotine and yellow stained fingers and nails

Auscultation

Auscultation might identify breath sounds more commonly associated with COPD:

- Rhonchi: sounds that resemble snoring that occur when air is blocked or becomes rough through the airways.
- Wheezing: high-pitched sounds produced by narrow airways that sometimes can be heard without a stethoscope.
- Diminished breath sounds

Laboratory

Arterial blood gasses (ABGs) provide information on pulmonary function and how well gas exchange is occurring. Hypoxemia is low PaO_2 (partial pressure of oxygen) in the blood. Hypercapnia is high $PaCO_2$ (partial pressure of carbon dioxide) and indicates hypoventilation [7]. There is no specific blood test to measure whether inadequate oxygen is being delivered to tissues (hypoxia). However, chronic hypoxia can stimulate increased production of red blood cells to carry more oxygen. This manifests

Table 16.1 Normal arterial blood gases [7]

Arterial blood	Normal (range)
pH	7.4 (7.35–7.45)
PaO_2	80–100 mm Hg (10.6–13.3 kPa)
$PaCO_2$	35–45 mm Hg (4.7–6.0 kPa)
SaO_2	95%

PaO_2 partial pressure of oxygen, *$PaCO_2$* partial pressure of carbon dioxide, *SaO_2* saturation of arterial oxygen, *kPa* kilopascal

as "polycythemia" or elevated hematocrit and/or hemoglobin. Table 16.1 depicts the normal ranges for ABGs.

Imaging

If available, chest x-ray might show hyperinflation and depressed diaphragm.

PK is over 40 years old and said she quit smoking 10 years ago. She has been coughing regularly over the last several months and sometimes brings up phlegm. PK should be referred for spirometry, as this test is the "gold standard" and required to establish a COPD diagnosis.

Diagnosis

Spirometry

Spirometry is a commonly used test to assess pulmonary function. It assesses how much and how quickly air can be expelled from the lungs. It helps to differentiate obstructive (air cannot get out) and restrictive (air cannot get in) lung disease by measuring lung volumes. All lung volumes are compared to normal values from healthy subjects (predicted values). The test itself takes about 15–20 minutes and carries no risk to patients (see standard spirometry volume/time curve, Fig. 16.1) [8]. Postbronchodilator forced expiratory volume over 1 second (FEV_1) over forced vital capacity (FVC) ratio (FEV_1/FVC) of less than 0.70 confirms the presence of an obstructive disorder.

PK was referred for diagnosis, and spirometry reveals an FEV_1/FVC ratio of 0.56, which is less than 0.70 and confirms the presence of persistent airflow limitation/obstruction.

The World Health Organization launched the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2001 [1]. These international strategies are updated annually based on the most recent evidence. The Canadian Thoracic Society (CTS) provided a 2017 position

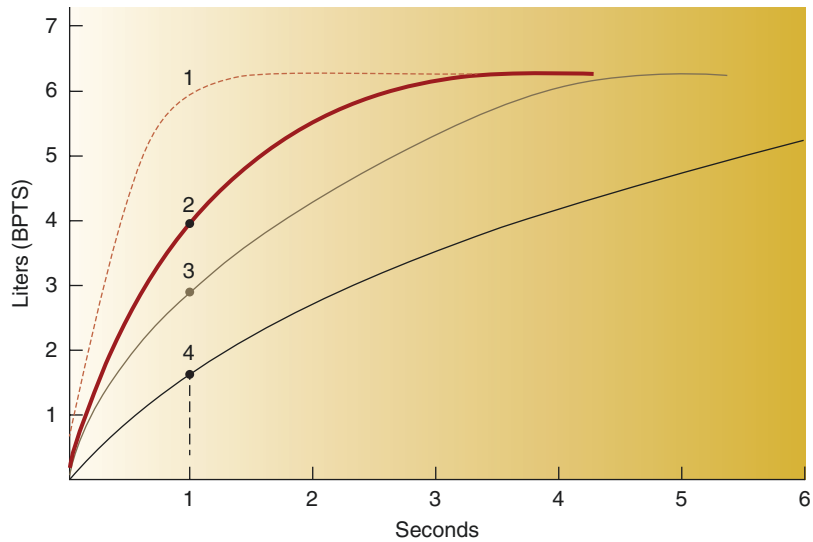


Fig. 16.1 Standard spirometry. Curve 1 is for a normal subject with normal forced expiratory volume over 1 second (FEV_1); curve 2 is for a patient with mild airway obstruction; curve 3 is for a patient with moderate airway obstruction; curve 4 is for a patient with severe airway obstruction. BPTS, body temperature saturated with water vapor. (Reprinted with permission from McGraw-Hill Education. Velez et al. [8]. Available at: https://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146078873. Accessed: July 30, 2018)

Table 16.2 Classification of airflow obstruction in COPD [1, 2, 4]

Degree of impairment	Spirometry
Mild	FEV_1 is greater than or equal to 80% predicted
Moderate	FEV_1 is greater or equal to 50% predicted and less than 80% predicted
Severe	FEV_1 is greater or equal to 30% predicted and less than 50% predicted
Very severe	FEV_1 is less than 30% predicted

FEV1 post-bronchodilator forced expiratory volume over 1 second

statement update for pharmacotherapy in COPD [6]. Other international guidelines offer similar recommendations. Readers should refer to the most recent evidence-based guidelines to direct care. The GOLD 2017 Strategy recommends assessment of lung function. In addition to being required for diagnosis (FEV_1/FVC), spirometry provides baseline FEV_1 [4]. Postbronchodilator FEV_1 indicates the degree of airflow obstruction or limitation (impairment of lung function) and is recommended to be repeated annually as a measure of disease progression (Table 16.2) [4]. There is a poor correlation between FEV_1, symptom intensity, exercise capacity, and quality of life. The most recent GOLD Strategy (2017) no longer includes FEV_1 as a factor in exacerbation risk assessment [4]. Degree of airflow obstruction or limitation is categorized as shown in Table 16.2 [1, 2, 4].

ABCD Classification

The GOLD Strategy recommends assessment of *frequency of exacerbations* and *severity of symptoms* to determine the ABCD classification of patients with COPD, which stratifies patients by risk of exacerbations and symptoms, to assist in directing initiation of pharmacologic care (Table 16.3).

Frequency of Exacerbations If there have been two or more exacerbations in the last 12 months or at least one exacerbation leading to hospital admission, the patient is considered at "higher risk" for exacerbations [4].

Table 16.3 GOLD 2017 ABCD Classification of patients with COPD based on exacerbation history and symptoms [4]

History of exacerbations	ABCD classification	
Higher risk (two or more exacerbations in the last 12 months or at least one leading to hospital admission)	C	D
Low risk	A	B
Symptom assessment	mMRC 0–1 (1–2 MRC) or CAT < 10 less symptoms	mMRC > 2 (>3 MRC) or CAT > 10 more symptoms

CAT COPD Assessment Test, *mMRC* modified Medical Research Council dyspnea scale, *MRC* Medical Research Council dyspnea scale

Symptom Severity There are a number of different tools that can be used to measure symptom severity. The most commonly used tools are the modified Medical Research Council (mMRC) or Medical Research Council (MRC) dyspnea scale and the COPD Assessment Test (CAT).

- MRC and mMRC dyspnea scales classify patients according to the severity of symptoms (Table 16.4). The Canadian Thoracic Society (CTS) Guidelines use the MRC scale, (1–5), whereas the GOLD Strategy uses the modified scale from 0 to 4 [2, 4].
- CAT includes eight statements about symptoms and activities. The patient scores each statement on a scale of 1–5. The impact of COPD symptoms is assessed by a cumulative score (0–40) [1]. CAT can found at http://www.catestonline.org.
- Patients with mMRC score of 0–1 (1–2 MRC scale) or a CAT score of less than 10 are considered to have "less symptoms." If patients have mMRC score of 2–4 (3–5 MRC scale), they are considered to have "more symptoms."

PK has an FEV1 67% (predicting moderate lung function impairment) with no exacerbations in the last year (low risk). She is breathless with moderate exercise (mMRC score = 0 (MRC = 1), few symptoms). Therefore, PK would be classified as risk Group A.

Table 16.4 GOLD mMRC and CTS MRC dyspnea scoring scale and corresponding definition [2, 4]

GOLD mMRC scoring	CTS MRC scoring	Definition
Grade 0	Grade 1	Breathless with strenuous exercise
Grade 1	Grade 2	Shortness of breath when hurrying on the level or walking up a slight hill
Grade 2	Grade 3	Slower than people of the same age on the level or stops for breath when walking at own pace on the level
Grade 3	Grade 4	Stops for breath after walking about 100 yards (90 meters) or after a few minutes on the level
Grade 4	Grade 5	Too breathless to leave the house or breathless with dressing

GOLD Global Initiative for Chronic Obstructive Lung Disease, *mMRC* modified Medical Research Council dyspnea scale, MRC Medical Research Council dyspnea scale

Table 16.5 COPD goals of therapy [1, 5]

Symptoms	Alleviate breathlessness and other respiratory symptoms Improve exercise tolerance and daily activity Improve overall health status
Risk	Prevent disease progression Reduce the frequency and severity of exacerbations Treat exacerbations and complications of the disease Reduce mortality

Management

COPD goals of therapy are to manage symptoms and reduce risks as described in Table 16.5. Management involves pharmacologic and non-pharmacologic measures for both prevention and treatment. Prevention strategies include [1, 2]:

- *Smoking cessation*: is beneficial at any stage of COPD (with or without pharmacologic intervention).
- *Vaccinations*: pneumococcal and annual influenza vaccinations.
- *Supplementary oxygen*: goal is to maintain oxygen saturation greater than 90%.
- *Avoiding drugs that exacerbate COPD*: these include antitussives, sedating antihistamines, and beta-blockers. Opioids and benzodiazepines should also be avoided, if possible, but may be used as part of end-of-life care.
- *Education and pulmonary rehabilitation*: patients should be educated on COPD and proper use of inhaler devices. They should be encouraged to have a healthy lifestyle and be referred to a pulmonary rehabilitation program.
- Currently, the use of prophylactic antibiotics to prevent exacerbations of COPD is controversial.

Pharmacological management of COPD primarily includes inhaled bronchodilators including beta-agonists (short-acting "SABA" and long-acting "LABA") and muscarinic antagonists (short-acting "SAMA" and long-acting "LAMA"). Figure 16.2 depicts the CTS COPD treatment pyramid [6], and Table 16.6 outlines the different classes of drugs utilized in the management of COPD. Controversy surrounds the use of low dose inhaled corticosteroids (ICS) as add-on treatment as they carry the potential for side effects such as pneumonia and cataracts [6]. ICS should never be used as monotherapy for COPD. When ICS/LABA combinations are used, high doses of ICS are not required to achieve optimum benefit. Oral therapies such as systemic steroids are used short term for exacerbations. Oral phosphodiesterase inhibitors, methylxanthines, and mucolytics are reserved for patients not responding to inhaled therapy as they also have the potential for significant side effects. The 2017 Canadian Thoracic Society Guidelines (Fig. 16.3) [6] mirror the GOLD approach of stepping up or stepping down drug management if symptoms fail to improve or continue to progress [4]. Initial therapy recommendations from GOLD and the CTS is presented in Table 16.7.

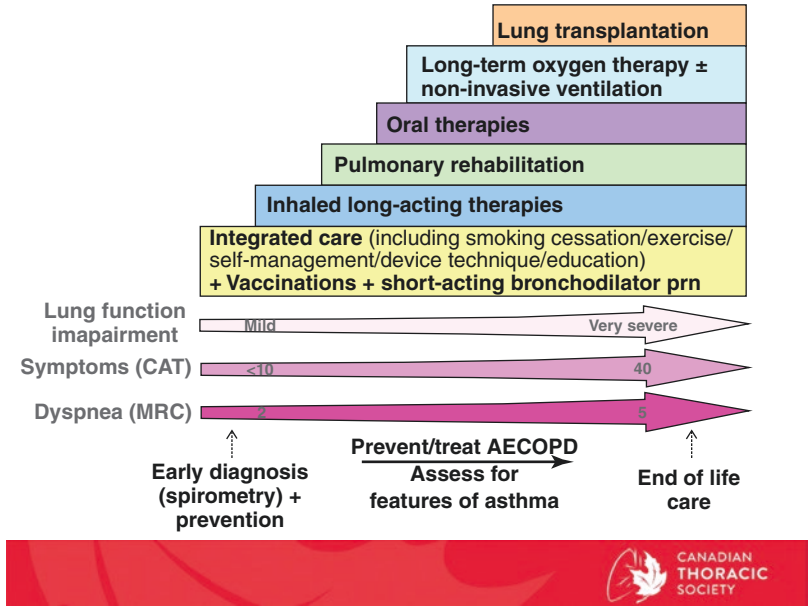


Fig. 16.2 COPD pyramid for comprehensive Management of COPD. Integrated approach of care that includes COPD diagnosis with spirometry, evaluation of symptom burden and risk for future exacerbations with ongoing monitoring, assessment for features of asthma, and comprehensive management, both nonpharmacologic and pharmacologic. CAT, COPD assessment test; MRC, Medical Research Council; SABD PRN, short-acting bronchodilator as needed; AECOPD, acute exacerbation of COPD; Inhaled Long-Acting Therapies, long-acting muscarinic antagonist and/or long-acting beta2-agonist and/or inhaled corticosteroid; LTOT, long-term oxygen therapy. (Reprinted from Bourbeau et al. [6]. With permission from Taylor & Francis Ltd., http://www.tandfonline.com)

Table 16.6 Classes of drugs used in the management of COPD

Drug class	Drug names (available delivery mechanism)
Inhaled beta-agonists	
Short-acting (SABA) Long-acting (LABA)	Salbutamol (MDI, Dk, Neb), terbutaline (TH) Formoterol (TH, Aerolizer – Inh Caps), Salmeterol (Dk), indacaterol (BH) Olodaterol (Rs) Not available as single agent: vilanterol
Inhaled muscarinic antagonists	
Short-acting (SAMA) Long-acting (LAMA)	Ipratropium (MDI, Neb) Tiotropium (HH, Rs), glycopyrronium (BH), aclidinium (PI), umeclidinium (E)
Inhaled combination beta-agonists/muscarinic antagonists	
Short-acting (SABA/SAMA) Long-acting (LABA/LAMA)	Salbutamol/ipratropium (Neb, Rs) Formoterol/aclidinium (PI) Olodaterol/tiotropium (Rs) Indacaterol/glycopyrronium (BH) Vilanterol/umeclidinium (E)
Inhaled combination beta-agonists/corticosteroids	
Long-acting (LABA/ICS)	Salmeterol/fluticasone propionate (Dk) Formoterol/budesonide (TH) Vilanterol/fluticasone furoate (E)
Phosphodiesterase inhibitors	Roflumilast capsules – oral
Methylxanthines	Theophylline, – oral, aminophylline - intravenous
N-acetylcysteine	Oral N-acetylcysteine: the injectable solution is administered orally, or powder could be compounded into capsules

BH Breezehaler, *Dk* Diskus, *E* Ellipta, *HH* HandiHaler, *Inh Caps* inhaled capsules, *MDI* metered dose inhaler, *Neb* nebule, *PI* Pressair inhaler, *Rs* Respimat, TH Turbuhaler

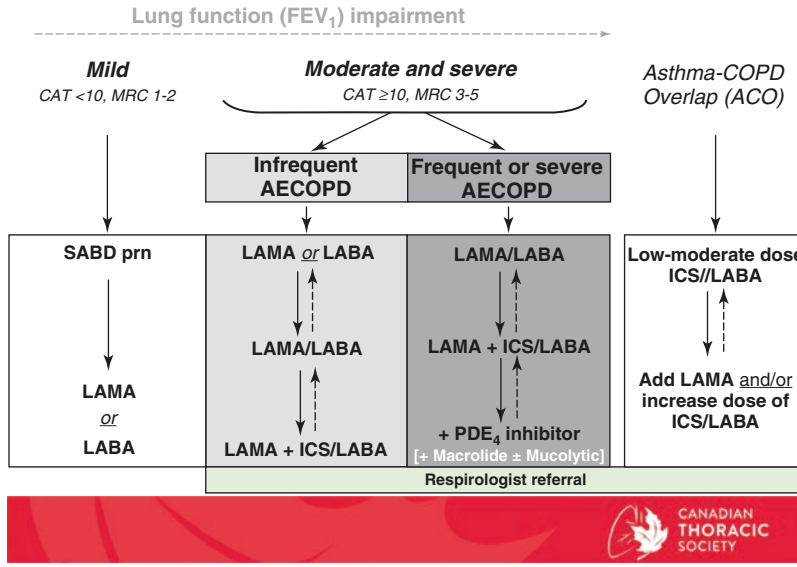


Fig. 16.3 COPD pharmacotherapy. Suggested COPD pharmacotherapy promoting an approach that matches treatment decisions with symptom burden and risk of future exacerbations. Solid arrows indicate step up therapy to optimally manage symptoms of dyspnea and/or activity limitation, as well as the prevention of AECOPD where appropriate. Dashed arrows indicate potential step down of therapy, with caution, and with close monitoring of the patient symptoms, exacerbations, and lung function. Frequent AECOPD is ≥2 events requiring antibiotics ± systemic corticosteroids over 2 years or ≥ 1 severe AECOPD requiring hospitalization. As-needed (prn) use of short-acting bronchodilator should accompany all recommended therapies. CAT, COPD assessment test; MRC, Medical Research Council; SABD prn, short-acting bronchodilator as needed; AECOPD, acute exacerbation of COPD; LAMA, long-acting muscarinic antagonist; LABA, long-acting B2-agonists; ICS, inhaled corticosteroid; PDE4, phosphodiesterase-4. (Reprinted from Bourbeau et al. [6]. With permission from Taylor & Francis Ltd., http://www.tandfonline.com)

Table 16.7 COPD initial pharmacotherapy based on ABCD classification (GOLD and CTS recommendations)

Classification of risk Group (GOLD) [4]	Initial therapy (GOLD 2017) [4]	CTS COPD 2017 update [6]
A Low-risk, less symptoms	SABD as needed or LABD	SABD as needed or LABD
B Low-risk, more symptoms	LABA or LAMA	LAMA is superior to LABA
C High-risk, less symptoms	LABA/LAMA	Prefer step up to LABA/LAMA over LABA/ICS in patients who do not have asthma overlap syndrome
D High-risk, more symptoms	LABA/LAMA/ICS	In patients with high symptom burden and poor health despite LABA/LAMA dual therapy – triple therapy may be considered Consider oral therapies when the patient is experiencing exacerbations despite optimized inhaled therapies

CTS Canadian Thoracic Society, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *SABD* short-acting bronchodilator, *LAMA* long-acting bronchodilator, *LABA* long-acting beta-agonist, *LAMA* long-acting muscarinic antagonist, *ICS* inhaled corticosteroid

As PK is in risk Group A and is not currently on any therapy, it would be appropriate to initiate short-acting bronchodilator (SABD) therapy and monitor frequency of use and response.

Follow-Up Assessment

In order to optimize therapy, ongoing follow-up should occur regularly to monitor efficacy, exacerbations, adverse effects, and most importantly adherence.

Adherence

One of the most common problems with inhalers is adherence and appropriate inhaler technique. Incorrect inhaler use is a potential obstacle to achieving good COPD control [6]. Patients should be assessed at each refill for *how* and *when* they are using their inhalers to ensure optimal drug therapy [4]. There are many alternative inhaler devices available that allow for modification of therapy based on the patient's ability to administer medications [9]. When assessing adherence, consider the patient's manual dexterity to load capsules into inhaler devices and ability to take deep breaths to inhale dry powders. Consider coordination of hand and breaths when using a metered dose inhaler (MDI) and if a valved holding chamber (VHC) is appropriate. Other questions to consider are whether once daily versus twice daily dosing is important and if the patient is better able to manage more than one inhaler type (i.e., MDI versus Turbuhaler versus Breezehaler). Table 16.8 provides examples of different types of delivery devices.

Table 16.8 Examples of available inhaler devices per drug and drug class [9]

Type of delivery	Type of device	Drug name	Drug class
Aerosolized (doses in a canister)	MDI (it can be used with valved holding chamber with or without mask)	Salbutamol Ipratropium	SABA SAMA
Dry powder (doses in a reservoir)	Turbuhaler	Terbutaline Formoterol Formoterol/ budesonide	SABA LABA LABA/ ICS
Dry powder (doses as single blisters within the device)	Diskus	Salbutamol Salmeterol Salmeterol/ fluticasone propionate	SABA LABA LABA/ ICS
	Pressair	Aclidinium Formoterol/ aclidinium	LAMA LABA/ LAMA
	Ellipta	Umeclidinium Vilanterol/ umeclidinium Vilanterol/ fluticasone furoate	LAMA LABA/ LAMA LABA/ ICS
Dry powder (doses as capsule to be loaded and punctured)	Aerolizer	Formoterol	
	HandiHaler	Tiotropium	LAMA
	Breezehaler	Indacaterol Glycopyrronium	LABA LAMA
Soft mist (doses in a canister)	Respimat	Salbutamol/ ipratropium Olodaterol/ tiotropium Tiotropium Olodaterol	SABA/ SAMA LABA/ LAMA LAMA LABA

MDI pressurized metered dose inhaler, *SABA* short-acting beta-agonist, *SAMA* short-acting muscarinic antagonist, *LABA* long-acting beta-agonist, *LAMA* long-acting muscarinic antagonist

Control

Signs and Symptoms

Assess if there have been any changes to symptoms from baseline (cough, sputum production, dyspnea, etc.) and severity using the same scale used previously (MRC, mMRC, CAT). COPD is a progressive disease therefore, overtime, it is expected that the patient will require more therapy to control symptoms, especially if underlying modifiable risk factors are not addressed (i.e., smoking cessation).

COPD Action Plan

All patients with COPD should have an individualized action plan (https://cts-sct.ca/wp-content/uploads/2018/03/4915_THOR_COPDActionPlanUpdate_Editable_Eng_v006.pdf). The COPD action plan includes information on what the usual daily symptoms look like for the patient (sputum color and level of activity) and what to do if there is a change in usual symptoms over at least 2 days. Action strategies include increasing use of the short-acting bronchodilator, a prescription for an antibiotic for sputum changes, and a short course of oral prednisone for increased shortness of breath. It also provides guidance on when to seek urgent or emergency care.

Adverse Drug Reactions

Table 16.9 lists the adverse reactions of drug therapy in patients with COPD.

Disease Complications

Acute Exacerbation of COPD

An acute exacerbation of COPD (AECOPD) has been likened to a "lung attack," where an exacerbation is to COPD what a myocardial infarction is to coronary artery disease [6]. It is an acute event with worsening of symptoms that are beyond the day-to-day normal variation [1]. Goals of therapy for AECOPD are to prevent hospitalization, acute respiratory failure, and death and to return symptoms to baseline [1].

Classification

Spirometry tests are not useful in the management of an AECOPD. AECOPD is classified according to the presenting symptoms. Patients presenting with three cardinal symptoms are considered to have a severe AECOPD, while those presenting with two cardinal symptoms have a moderate AECOPD [1]. Cardinal symptoms include:

Table 16.9 List of adverse reactions of drug therapy in patients with COPD

Drug	Common adverse reactions/precautions
Beta-agonists [10]	Tremors, headache, dizziness, sleep disturbances, nausea Hypokalemia, sinus tachycardia, and rhythm disturbances in predisposed individuals
Muscarinic antagonists [11]	Dry mouth, metallic taste, blurred vision Urinary retention, caution in narrow angle glaucoma, severe cardiovascular disorders (arrhythmias)
Inhaled corticosteroids [12]	Oropharyngeal candidiasis, dysphonia, cough Systemic side effects (adrenal insufficiency, skin thinning, osteoporosis) with long-term high-dose usage
Phosphodiesterase inhibitors (roflumilast) [13]	Nausea, diarrhea, weight loss, headache, decreased appetite, dizziness, insomnia, anxiety Neuropsychiatric effects (potential for suicidal thoughts, worsening depression)
Methylxanthines (theophylline) [14]	Anorexia, nausea, vomiting, abdominal cramps, headaches, nervousness, tremor, insomnia Toxicity associated with theophylline serum concentrations >110 umol/L Notable drug interactions: antibiotics (ciprofloxacin, norfloxacin, erythromycin), antiepileptics (carbamazepine, phenytoin), smoking, allopurinol, fluvoxamine
Oral/systemic corticosteroids [15]	*Short-term use* Hypertension, weight gain (due to sodium/water retention), hyperglycemia, nausea, mood changes, insomnia, appetite stimulation, leukocytosis, flushing *Long-term use* Cushing's syndrome, adrenal suppression, gastrointestinal ulcerations, osteoporosis, cataract

- Worsening of dyspnea
- Increase in sputum volume
- Increase in sputum purulence

A mild AECOPD presents with one of the cardinal symptoms above plus at least one of the following:

- Upper respiratory tract infection in the last 5 days
- Fever without other explanation
- Increased wheezing
- Increased cough
- Increase in respiratory rate or heart rate (20% above baseline)

Management of AECOPD [1, 4]
Management of AECOPD will depend on the severity of the exacerbation. Severe AECOPD requires hospital admission. Nonpharmacologic management may include oxygen with a target oxygen saturation of 88–92%. Noninvasive or invasive mechanical ventilation may be required for acute respiratory failure. In moderate to severe AECOPD, pharmacologic management includes adding regularly scheduled short-acting bronchodilators and systemic corticosteroids (i.e., oral prednisone 30–50 mg daily for 5–10 days) to ongoing long-acting bronchodilators. Consider antibiotic use in patients with two or more cardinal symptoms [1].Refer to local guidelines for choice of antibiotic therapy. In mild AECOPD, treatment involves an increase in SABD therapy.

Long-Term Complications

As the disease progresses, and if not managed, the patient may develop secondary pulmonary hypertension, which can result in cor pulmonale (right-sided heart failure). As this a progressive disease, patients can move on to respiratory failure and death [1].

Clinical Pearls

- Pharmacists play an important role in the identification and management of patients with COPD.
- Suspect COPD in smokers over 40 years of age and refer for diagnosis.
- As drugs within a class (i.e., LABA) have similar efficacy, patient factors such as ability to manage inhaler device, frequency of dosing, and cost should guide drug choice within a therapeutic class.
- Assessment at follow-up visits (refills) includes review of inhaler technique and use, evaluation of how well the therapy is managing the patient's symptoms and improving quality of life, frequency of exacerbations, and adverse effects.
- Ensure each COPD patient has an action plan and knows what to do in case of an exacerbation.

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Epilepsy

17

Sherif Hanafy Mahmoud

Chapter Objectives

1. Describe the epidemiology, etiology, risk factors, and pathophysiology of epilepsy.
2. Describe the classification of different seizure types.
3. Conduct initial assessment of patients newly diagnosed with epilepsy.
4. Apply the general principles of antiepileptic drug therapy in the follow-up assessment of patients with epilepsy.

Background

Epilepsy is a neurological condition characterized by the occurrence of epileptic seizures. It is important to differentiate seizures from epilepsy. A seizure is "a symptom" of an illness, while epilepsy is a disease. Seizures or spells have been defined by the International League Against Epilepsy (ILAE) as "A transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal activity in the brain" [1]. Seizures can be provoked secondary to a mechanical or metabolic insult to the brain or can be unprovoked. If a patient experienced more than one unprovoked seizure more than 1 day apart and/or is at high risk of experiencing further unprovoked seizures, he or she is considered to have epilepsy. In addition, patients who have a constellation of symptoms where epileptic seizures are a common occurrence (epilepsy syndromes such as Lennox-Gastaut syndrome) are considered to have epilepsy [2]. While 10% of the population will experience a seizure at some time point, the prevalence of epilepsy ranges from 500 to 1000 per 100,000 population. Around 0.6% of Canadians are diagnosed with epilepsy with an annual incidence of 50 per 100,000 population. The highest incidence of epilepsy occurs at ages younger than 10 and older than 60 years. Furthermore, three quarters of epilepsy diagnoses begins before the age of 18. Epilepsy has a great impact on the patients' quality of life. Patients with epilepsy might have their independence compromised, high unemployment rate, and tend to be socially isolated. For example, patients with uncontrolled seizures lose their driving privileges, unable to swim alone or care for their children by themselves. Pharmacists play an important role in the management of patients with epilepsy. They are able to assess the patients for the presence of any clinically significant drug interactions, adverse reactions, and red flag symptoms secondary to the antiepileptic drug therapy. In addition, they aid in the interpretation of antiepileptic drug levels (therapeutic drug monitoring).

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Classification of Seizure Types

According to the 2017 ILAE seizure classification, seizures are classified into three main classes: seizures with focal, generalized, and unknown onset (Fig. 17.1) [3]. Generalized seizures account for approximately 30% of seizure types, while focal seizures account for 70% of seizures. Compared to generalized seizures, focal seizures (formerly called partial seizures) involve only a certain part of the brain. They are further classified according to the patient's awareness and the presence or absence of motor and other symptoms. Based on patient's awareness, focal seizures are categorized into focal seizures with intact awareness (simple partial seizures) and focal seizures with impaired awareness (complex partial seizures). In simple partial seizures, patients are usually aware of their surroundings and the seizures typically last for less than 60 seconds. Those seizures could be motor such as muscle twitching, sensory, and/or an autonomic. On the other hand, complex partial seizures are associated with altered level of consciousness and behavioral arrest. They typically last for 1–2 minutes followed by postictal confusion. Motor automatism such as chewing movement or lip smacking is a relatively common feature in patients exhibiting complex partial seizures. Furthermore, focal onset seizures could progress into generalized seizures in some patients (secondarily generalized).

In generalized seizures, there is a widespread involvement of the brain, and seizures could be convulsive (motor involvement) or non-convulsive (non-motor). The most common motor generalized seizure is the generalized tonic-clonic convulsion (GTC, formerly called grand-mal seizure). GTC is typically associated with loss of consciousness with hyperextension of the body followed by rhythmic full body contractions (tonic and clonic phases, respectively). GTC generally lasts for 1–2 minutes followed by postictal confusion, stupor, and headache. On the other hand, the most common non-motor generalized seizure is the typical absence seizure (previously known as petit-mal seizure). It is more common in children than adults, and it is characterized by sudden and brief impairment of awareness lasting for several seconds. Myoclonic seizures are another form of generalized seizures that are characterized by sudden brief muscle contractions (milliseconds) without loss of consciousness. Awareness of the patient's seizure type is essential because some drugs are not effective or even may aggravate certain seizure types. For example, phenytoin

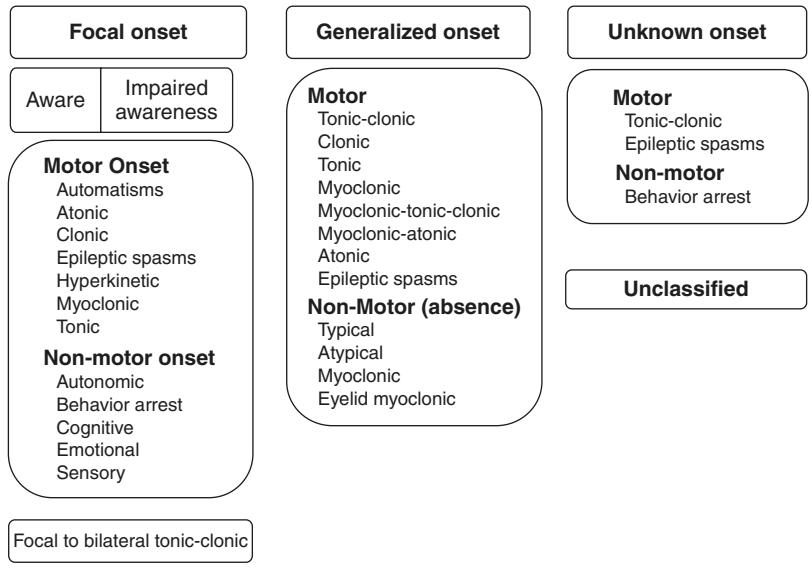


Fig. 17.1 Operational classification of seizure types by the International League Against Epilepsy. (Reprinted from Fisher et al. [3], with permission from John Wiley and Sons)

and carbamazepine are not effective in controlling myoclonic and absence seizures.

Etiology and Risk Factors

A wide range of etiologies have been implicated to cause seizures and epilepsy:

- Genetic causes
- Traumatic brain injury
- Central nervous system infections, e.g., meningitis and encephalitis
- Progressive CNS diseases such as brain tumors and Alzheimer disease
- Metabolic derangements, e.g., hypoglycemia, hyponatremia, and uremia. Because laboratory abnormalities could precipitate seizures, it is important to rule them out while assessing patients presenting with seizures.
- *Drugs and their withdrawal*: Numerous drugs could precipitate or aggravate seizures in patients with epilepsy. These include illicit drugs and drugs prescribed for various illnesses. Pharmacists need to be aware of these drugs when assessing patients presenting with seizures or have a history of epilepsy. Table 17.1 summarizes drugs potentially implicated to lower seizure threshold in susceptible individuals. To illustrate, Fig. 17.2 depicts drugs implicated to have caused seizures in a retrospective study of 386 cases of drug-induced seizures in the state of California, USA [4]. It is worth to mention that bupropion, an antidepressant, was the most commonly implicated drug to precipitate seizures. Therefore, bupropion should be avoided, if possible, in patients with a history of seizures and epilepsy. In addition to drug-induced seizures, other agents could precipi-

Table 17.1 Drugs potentially implicated to lower seizure threshold in susceptible individuals

Drug class	Examples
Antidepressants	Generally, all antidepressants might lower the seizure threshold and should be used with caution in patients with history of seizures and epilepsy Bupropion is highly implicated to aggravate seizures
Antipsychotics	Quetiapine; haloperidol
Immunosuppressives	Tacrolimus; cyclosporine
Illicit drugs	Amphetamines; cocaine
Antimicrobial agents	Beta-lactam antibiotics; fluoroquinolones; acyclovir (generally if given at high doses in patients with impaired renal function)
Analgesics	Tramadol, meperidine

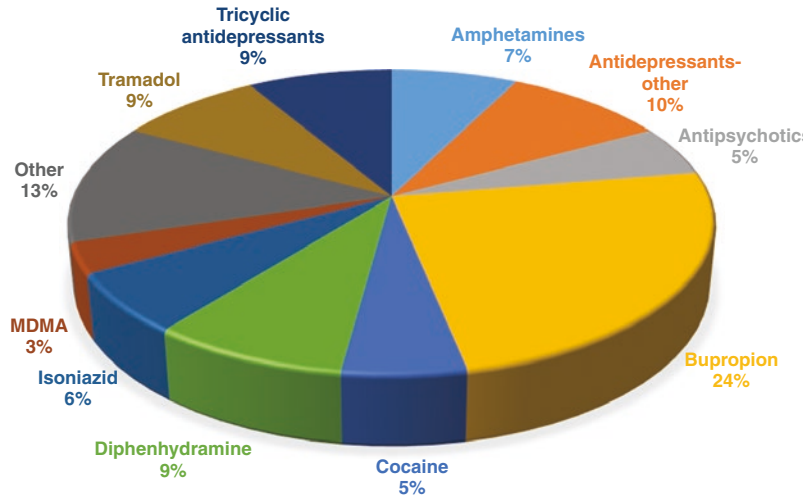


Fig. 17.2 Breakdown of drug-induced seizure by drug type. MDMA, methylenedioxymethamphetamine. (Reprinted by permission from Springer Nature: Thundiyil et al. [4], Copyright 2007)

tate seizures if withdrawn abruptly such as in the case of benzodiazepines and alcohol withdrawal.
- Additional risk factors could precipitate or aggravate seizures in susceptible individuals such as fatigue, sleep deprivation, flickering lights, and stress. These factors need to be taken into consideration when assessing patients with epilepsy.

Diagnosis

History is the most important component in diagnosis. Witnesses are usually asked to describe what happened exactly with the timing, if possible, and if there is any associated postictal confusion. It is suggested not to ask the witnesses to name the seizure as they might be mistaken. In addition to describing the spell, the following could be helpful in assessing patients presenting with seizures:

- Presence or absence of auras
- Circumstances surrounding the seizure that could have precipitated the event
- History of drug or alcohol abuse
- Past history of childhood epilepsy and childhood illnesses such as meningitis, encephalitis, and febrile seizures
- Past history of head injury, stroke, brain tumor, or any systemic conditions that might affect CNS and may precipitate seizures

Physical examination is often not helpful as it happens after the seizures have subsided. The clinician can look for evidence of tongue biting, incontinence, postictal confusion, and any evidence of neurological symptoms. In addition, a comprehensive lab panel looking for any precipitating factors should be done to rule out seizures secondary to electrolytes and metabolic derangements such as hypoglycemia and hyponatremia. Additional diagnostic modalities which include electroencephalography (EEG) (however, it's normal in 20% of patients) and imaging such as head computed tomography (CT) and magnetic resonance imaging (MRI) are utilized for differential diagnosis.

Pathophysiology

Normal neuronal activity is usually non-synchronized. In other words, some neurons are inhibited and other are excited during the relay of information throughout the brain. Seizures occur when neurons are activated synchronously. To simplify this, seizures are the result of an imbalance between excitatory and inhibitory mechanisms. Examples of these excitatory mechanisms include activation of the excitatory glutamate receptors and enhanced sodium and calcium influx into the neurons. On the other hand, inhibitory mechanisms involve inhibition or malfunction of the gamma aminobutyric acid (GABA) neurotransmission and potassium channels. This imbalance could be caused by genetic mutations leading to ion channels defect (genetic etiology of epilepsy) or secondary to an insult to the brain as in the case of traumatic brain injury or stroke. The use of antiepileptic drugs (AEDs) aims to re-establish the balance between the inhibitory and excitatory transmission by either augmenting inhibitory mechanisms or inhibiting excitatory mechanisms.

Management

Patients with epilepsy should have individualized goals of therapy tailored to fit their seizure type, etiology, comorbidities, personal preference and lifestyle. Ideally, complete seizure freedom is the ultimate goal; however, despite advances in epilepsy management, almost one-third of patients fail to achieve complete seizure freedom. Therefore, in some patients, the goal is reducing the frequency of seizures, by a certain percentage, rather than achieving complete seizure control. A balance between seizure control and adverse effects of antiepileptic drugs needs to be maintained with an ultimate goal to improve the patient's quality of life. Treatment

goals need to be reviewed and revised at every follow-up visit.

Non-pharmacological measures include counseling patients to avoid seizure triggers such as sleep deprivation and heavy alcohol intake. In addition, patients need to be advised to consult their pharmacist or healthcare provider when starting or stopping any over the counter medications and herbal supplements as those might have the propensity to aggravate seizures or interact with the patient's antiepileptic drugs. Other non-pharmacological management includes the use of ketogenic diet, vagus nerve stimulation, epilepsy surgery, and medical marijuana.

Pharmacological management typically involves the use of antiepileptic drugs. These agents aim to re-establish the balance among inhibitory and excitatory mechanisms. They augment the inhibitory mechanisms by enhancing the inhibitory GABA neurotransmission or blocking the excitatory sodium channels, calcium channels, or glutamate receptors. Table 17.2 summarizes the different classes of antiepileptic drugs and their recommended adult dosage range. In addition to their classifications based on their mechanism of action, AEDs can be classified into old and new. Old AEDs are generally metabolized by the liver and prone to multiple drug interactions. On the other hand, new AEDs are generally renally eliminated and less susceptible to drug interactions.

Table 17.2 Classes of antiepileptic drugs (AEDs) used in the management of seizures

Drug Class	Individual AEDs and adult dosage range in patients with normal liver and kidney function
Sodium channel blockers	Phenytoin 4–7 mg/kg/day Carbamazepine 400–1200 mg/day Oxcarbazepine 600–2400 mg/day Eslicarbazepine 400–1600 mg/day Lamotrigine 50–500 mg/day Lacosamide 100–600 mg/day
SV2A modulators	Levetiracetam 1000–3000 mg/day Brivaracetam 50–200 mg/day
GABA-A receptor agonists	Clobazam 5–80 mg/day Clonazepam 1.5–20 mg/day Phenobarbital 2–3 mg/kg/day Primidone 250–2000 mg/day
Other GABA modulators	Vigabatrin 1000–3000 mg/day
T-type calcium channel blockers	Ethosuximide 500–1500 mg/day
AMPA receptor blockers	Perampanel 2–12 mg/day
Others/multiple mechanisms of actions	Valproic acid/divalproex 15–60 mg/kg/day Topiramate 200–400 mg/day Gabapentin 900–3600 mg/day Pregabalin 150–600 mg/day Rufinamide 400–3200 mg/day Stiripentol 50 mg/kg/day

AMPA receptor is a glutamate receptor, *GABA* gamma amino butyric acid, *SV2A* synaptic vesicle glycoprotein 2A

Initial Assessment of a Patient Newly Diagnosed with Epilepsy

Pharmacists play an important role in the management of patients with epilepsy. They are able to assess the patients for the presence of any clinically significant drug interactions, adverse reactions, and red flag symptoms secondary to the antiepileptic drug therapy. In addition, they aid in the interpretation of antiepileptic drug levels (therapeutic drug monitoring). AEDs are generally recommended in patients who experience two or more unprovoked seizures or experience seizures secondary to brain insults and are at high risk of experiencing further seizures. Similar to other medical conditions, proper initial assessment of patients newly diagnosed with epilepsy requires collection of a complete relevant history (demographics, history of present illness, medical history, social history, medications, compliance concerns, and physical examination findings). Initial assessment includes the following:

- *Assessment of the appropriateness of the selected antiepileptic drug given the patient's seizure type(s):* Assessment of the appropriateness of the AED involves making sure that the AED is effective for the patient's particular seizure type. AEDs are generally effective in many seizure types. However, many exceptions exist. To illustrate, due its unique mechanism of action, ethosuximide is only effective in controlling absence seizures. On the other

Table 17.3 Effectiveness of antiepileptic drugs (AEDs) in various seizure types

Seizure type	Active AEDs
Focal seizures	Generally, most of the available AEDs are active against focal seizures Phenytoin; phenobarbital; primidone; carbamazepine; eslicarbazepine; oxcarbazepine; lamotrigine; lacosamide; levetiracetam; brivaracetam; clobazam; perampanel; valproic acid/divalproex; vigabatrin; topiramate; gabapentin
Generalized tonic-clonic seizures	Phenytoin; carbamazepine; valproic acid; levetiracetam; lamotrigine; clobazam; topiramate; perampanel
Myoclonic seizures	Valproic acid/divalproex; levetiracetam; lamotrigine; topiramate; clobazam; rufinamide
Absence seizures	Ethosuximide; valproic acid/divalproex; lamotrigine; clobazam

hand, phenytoin and carbamazepine are ineffective and may aggravate absence and myoclonic seizures. Table 17.3 depicts a general outline of the effectiveness of AEDs in various seizure types. It is important to note that first-line recommendations vary among different guidelines [5].

- *Assessment of the appropriateness of the selected antiepileptic drug given the patient's characteristics:* Patients' age, sex, comorbidities, concomitant medications, plans for pregnancy, drug coverage, and adherence issues are very important factors that need to be considered in the initial assessment of patients with epilepsy. Table 17.4 summarizes the patients' specific factors that need to be assessed with individual AEDs.

Table 17.4 Summary of patient-specific factors that need to be taken into consideration with individual antiepileptic drugs

AED	Patient factors to be considered
All AEDs	*PMH*: caution in patients with hepatic and renal impairment *MH:* consult a drug interaction reference with any changes in patient's medications regimen *Pregnancy:* the lowest effective AED dose in pregnant women is recommended; monotherapy preferred; valproic acid should be avoided *SH:* caution with alcohol intake and to be avoided, if possible. Excessive intake should be avoided
Brivaracetam	*PMH*: caution in patients with psychiatric history, hepatic and renal impairment
Carbamazepine	*PMH*: caution in patients with hepatic impairment, hyponatremia, and cardiac diseases *Race*: Asians have increased propensity for SJS. HLA-B*1502 allele screening is recommended to determine the risk *MH*: it is a liver microsomal enzyme inducer. Always consult a drug interaction reference when it is initiated or a new drug added to existing regimens containing this AED
Clobazam	*PMH*: caution in patients with history of drug abuse (dependence risk) and hepatic impairment
Clonazepam	*PMH*: caution in patients with history of drug abuse (dependence risk), respiratory problems, hepatic and renal impairment. Avoid in patients with acute narrow angle glaucoma
Eslicarbazepine	*PMH*: caution in patients with hepatic and renal impairment. *MH*: it is a liver microsomal enzyme inducer. Always consult a drug interaction reference when it is initiated or a new drug added to existing regimens containing this AED *Coverage*: expensive
Gabapentin	*PMH:* caution in patients with renal impairment
Lacosamide	*PMH:* caution in patients with cardiac conduction problems (it causes PR interval prolongation), hepatic and renal impairment
Lamotrigine	*PMH*: caution in patients with renal and hepatic impairment. *MH*: slower titration schedule and lower target dose if the patient is on valproic acid. It has multiple drug interactions; consult drug interaction reference when lamotrigine gets started
Levetiracetam	*PMH*: caution in patients with psychiatric illnesses, behavioral problems, and renal impairment
Oxcarbazepine	*PMH*: caution in patients with hepatic and renal impairment *MH*: it is a liver microsomal enzyme inducer. Always consult a drug interaction reference when it is initiated or a new drug added to existing regimens containing this AED *Coverage*: expensive

Table 17.4 (continued)

AED	Patient factors to be considered
Perampanel	*PMH*: caution in patients with hepatic and renal impairment *Coverage*: expensive
Phenobarbital	*PMH*: caution in patients with hepatic and renal impairment, cardiac disease, diabetes, hyperthyroidism, and severe anemia *MH*: it is a liver microsomal enzyme inducer. Always consult a drug interaction reference when it is initiated or a new drug added to existing regimens containing this AED
Phenytoin	*PMH*: caution in patients with hepatic and renal impairment, cardiac disease, low albumin, and hyperthyroidism *Sex*: due to its long-term side effects, it is not a preferred agent for chronic use in females. It causes coarsening of facial features, hirsutism, and gingival hyperplasia *Dose titration note:* it exhibits non-linear pharmacokinetics: dose increases are not associated with proportional increase in drug level. Dose changes should not exceed 50–100 mg/day at a time *MH*: it is a liver microsomal enzyme inducer. Always consult a drug interaction reference when it is initiated or a new drug added to existing regimens containing this AED
Topiramate	*PMH:* caution in patients with history of renal stones, metabolic acidosis, hepatic and renal impairment
Valproic acid/divalproex sodium	*PMH*: caution in patients with hepatic and renal impairment *MH*: it is a liver microsomal enzyme inhibitor. Always consult a drug interaction reference when it is initiated or a new drug added to existing regimens containing this AED *Pregnancy*: avoid during pregnancy. The least favorable AED option in women in childbearing period

AED antiepileptic drug, *MH* medication history, *PMH* past medical history, *SJS* Stevens-Johnson syndrome

- *Assessment of the appropriateness of the dosage regimen of the selected AED:* Generally, patients start with an AED monotherapy at fraction of the target dose to minimize adverse reactions. Then, the dose gets titrated up based on the patient's tolerance and seizure control. The rate of the dose titration depends on the urgency for seizure control. If rapid seizure control is required as in the case of emergencies, some AEDs can be started directly at target dose. These include phenytoin, phenobarbital, valproic acid, and levetiracetam. However, if there is no urgency, it is preferable that all AEDs to be titrated slowly. On the other hand, other agents should be titrated slowly in order to avoid adverse reactions and enhance tolerance. For example, carbamazepine needs to be titrated slowly to avoid GI adverse reactions and drowsiness. Other examples include topiramate and lamotrigine. While topiramate slow titration potentially helps alleviating the cognitive impairment associated with its use, lamotrigine slow titration potentially protects against possible dermatological reactions that could be life threatening. If those agents are initiated at full dose, pharmacists might need to flag it to the prescriber for re-assessment.

Follow-Up Assessment

Adherence

Adherence in taking antiepileptic drugs as prescribed is very essential for proper seizure control. As with other conditions, pharmacists play an important role in promoting patient compliance. All the general factors that affect patient compliance such as knowledge of the disease, regimen simplification, and dose reminder tools apply to patients with epilepsy. One of the factors that could specifically affect adherence in epilepsy patients is the temptation to self-stop the AED if patient's seizures are well controlled for a while. Patients need to be aware that they should not stop their medications without consulting their neurologist. Abrupt stop of AED medications might lead to withdrawal seizures and even might lead to status epilepticus, a life-threatening

medical emergency. Neurologists might assess titrating down AEDs if the patients are seizure-free for 2 or more years for epilepsy with non-acquired causes or for 6–12 months for epilepsy secondary to acquired causes.

Control

Symptoms

It is important to assess seizure control and determine if patient's specific goals are achieved, e.g., complete seizure freedom or and 50% reduction in the frequency of seizures. If seizure control is not adequately achieved, other factors need to be assessed before judging therapy failure such as patient adherence, AED dose adequacy, presence of drug interactions, and presence of possible seizure triggers. In addition, worsening seizure control should prompt the pharmacist to refer the patient to seek medical attention especially if there is not apparent cause for the patient's worsening seizure control. If AED monotherapy fails to control patient's seizures, another monotherapy could be tried before adding a second agent (AED polytherapy). This approach will have the advantage of minimizing adverse reactions, avoiding drug interactions, better adherence, and less cost. In some patients, polytherapy might be needed especially if two or three monotherapy alternatives failed to control the patient's seizures.

Laboratory

In specialized practice settings, pharmacists might aid in the therapeutic drug monitoring of antiepileptic drugs. Many of the antiepileptic drugs have suggested reference ranges. A reference range is the range of drug concentrations below which the AED is most probably ineffective, and above which it is most probably toxic. It is important to mention that it is not carved in stone. To illustrate, the drug can be effective at concentrations below reference range, or toxic at concentrations within the reference range. Reference ranges can be used as a tool, rather than an ultimate target, as it is important to treat the patient, not the level. If we can measure a drug concentration, it does not mean that we need to measure it and routine levels are not recommended. Drug levels are usually measured at steady state. However, pre-steady state levels can be beneficial in some situations to determine the adequacy of the dosage. Drug levels need to be requested only if indicated. For example, the suggested reference range for total phenytoin concentration is 40–80 μmol/L. If a patient has no adequate seizure control while on phenytoin, measuring phenytoin concentration will be helpful to determine if there is a room to increase the dose. The following are the indications for AED level:

- Change in seizure frequency
- Suspected dose-related adverse reactions or toxicity
- Administration of multiple interacting drugs
- Checking adherence
- Formulation and/or route change
- Conditions of altered pharmacokinetics, e.g., elderly, pregnancy
- Determination of the individual's therapeutic range

Adverse Reactions

Pharmacists play an important role in monitoring how patients tolerate drug therapy. Monitoring AED therapy involves asking questions about adverse drug reactions and checking some laboratory test. AEDs' adverse reactions are divided into acute and chronic. Acute adverse reactions are the ones generally experienced by patients within the first few weeks of therapy. They are further divided into concentration-dependent where dose reduction results in amelioration of the symptoms and idiosyncratic. The latter are not dose-dependent and range from mild to life threatening. On the other hand, chronic adverse reactions are usually apparent with the long-term administration of AEDs. Table 17.5 summarizes the common adverse reactions, lab monitoring, and red flag complication of currently available AEDs.

Table 17.5 Common adverse reactions, lab monitoring, and red flag complications of individual antiepileptic drugs

AED	Symptoms and laboratory monitoring	Red flag complications (prompt referral)
All AEDs	*ADR:* Hypersensitivity reactions, drowsiness, dizziness, fatigue, ataxia, and symptoms of suicidal ideations *Lab*: LFT, CBC, SCr	DRESS Hypersensitivity reactions Suicidal ideations Hepatotoxicity Signs of AED toxicity, e.g., excessive sedation, ataxia
Carbamazepine, eslicarbazepine, oxcarbazepine	GI upset, blurred vision, diplopia, behavioral changes. Electrolytes; thyroid function Reference range 20–50 μmol/L Periodic eye examination	Bleeding Hematological abnormalities
Clobazam, clonazepam, phenobarbital	Behavioral changes and signs of dependence; changes in respiratory status Phenobarbital reference range 40–170 μmol/L	Signs of dependence Respiratory depression
Lacosamide	Symptoms of heart block (e.g., slow or irregular pulse, headache) ECG in patients at risk of cardiac disorders or on concomitant medications that prolong the PR interval	Symptoms of AV block
Lamotrigine	Close monitoring for dermatological reactions	Skin reactions Symptoms of meningitis Hematological abnormalities
Levetiracetam	Behavioral and psychiatric changes	Behavioral and psychiatric changes
Perampanel	Behavioral and psychiatric changes	Behavioral and psychiatric changes
Phenytoin	Nystagmus, slurred speech, blurred vision, confusion Gingival hyperplasia, hirsutism, acne, coarsening of facial feature Reference range: total 40–80 μmol/L; free 4–8 μmol/L	Hematological abnormalities
Topiramate	Weight loss; hydration status, sweating changes, or increased body temperature Serum bicarbonate Periodic eye examination	Renal stones Metabolic acidosis
Valproic acid/divalproex sodium	GI upset, tremors, weight gain Motor and cognitive function Serum ammonia Reference range 350–700 μmol/L	Hematological abnormalities Pancreatitis

ADR adverse drug reactions, *AED* antiepileptic drug, *CBC* complete blood count, *DRESS* dreug reaction with eosinophilia and systemic symptoms, *LFT* liver function tests, *SCr* serum creatinine

Complications

The main complication of epilepsy is worsening seizure control due to disease progression. In addition, patients might have injuries inflicted while they are seizing. In general, worsening seizure control secondary to no apparent causes should prompt referral.

Clinical Pearls

- Pharmacists play an important role in the management of patients with epilepsy.
- Initial assessment of patients with epilepsy involves assessment of the appropriateness of the selected antiepileptic drug given the patient's seizure type and patient's characteristics and assessment of the appropriateness of the dosage regimen of the selected AEDs.
- Assessment at follow-up involves exploring patient's adherence, seizure control, and the presence of any drug-related adverse reactions or toxicity.
- Pharmacists need to be aware of the rare but serious red flag complications of AEDs such as DRESS syndrome, blood abnormalities, liver failure, and suicidal ideations.

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Osteoporosis

18

Nese Yuksel and Theresa L. Charrois

Chapter Objectives

1. Assess fracture risk in patients using bone mineral density and risk factors.
2. Identify potential complications from osteoporosis drug therapy.
3. Assess appropriate monitoring parameters in osteoporosis including labwork and imaging.

Background

Osteoporosis is characterized by low bone mass and bone tissue deterioration leading to compromised bone strength and increased risk of fracture. Over 200 million people are affected by osteoporosis worldwide [1]. Osteoporosis affects both women and men, with approximately one in three women and one in five men at risk for an osteoporotic fracture in their lifetime [1]. Osteoporosis can occur from loss of estrogen in menopause and age-related changes in bone or from secondary causes such as certain disease or medications (Tables 18.1 and 18.2). The most common sites for osteoporosis fractures are in the wrist, spine, hip, and ribs. It is estimated that over 80% of all fragility fractures occurring in postmenopausal women are from osteoporosis [2]. A fragility fracture is defined as a low trauma fracture occurring from standing height or less. Fractures are associated with pain, disability, disfigurement, and loss of independence, as well as significant cost to the health care system. Once an individual sustains a fragility fracture, they are at increased risk for another fracture, with 2.5-fold increase risk of fracturing after a hip fracture and nearly 5-fold risk after vertebral fracture [3, 4]. Fractures are also associated with increased mortality. The risk of mortality in 1 year after a hip fracture in women is 28%, and this risk is even higher in men at 37% [5]. Despite the societal impact of fractures, a care gap with osteoporosis management exists with less than 20% of people who have had a fragility fracture receiving treatment [6].

Pathophysiology

Bone remodeling is a continuous process, which is tightly regulated resulting in a normal balance of bone resorption and bone formation for optimum bone strength. Any imbalance of the normal bone remodeling process can lead to excessive resorption or decreased bone formation leading to inadequately filled bone remodeling pits. If this process continues, this can result in lower bone mineral density and microarchitecture dete-

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Table 18.1 Risk factors for osteoporosis

Individual characteristics
Age (>50 years old)
Family history (especially parenteral hip fracture)
Personal history of fragility fracture after age 40 years
Vertebral fractures
Race/ethnicity (Caucasian, East Asian)
Early menopause (<45 years)
Low body weight or major weight loss
Lifestyle factors
Current smoker
Alcohol intake >3 or more drinks per day
Low calcium intake
Low vitamin D intake or deficiency
Low physical activity
High caffeine intake
Hypogonadal states
Women: early menopause (<45 years), premature ovarian insufficiency, previous amenorrhea (anorexia, athletic)
Men: Hypogonadism
Endocrine disorders
Hyperparathyroidism
Hyperthyroidism
Cushing's syndrome
Diabetes Type 1 and 2
Rheumatologic disorders
Rheumatoid arthritis
Systemic lupus
GI disorders
Celiac
Inflammatory bowel disease
Other malabsorption diseases
Other diseases/disorders
Chronic kidney diseases
COPD
HIV
Malignancies (i.e., multiple myelomas, leukemia, lymphoma)

COPD chronic obstructive pulmonary disease, *GI* gastrointestinal

rioration, leading to increased risk of fracture. The bone remodeling process is complex and is controlled by various hormones (i.e., estrogen, testosterone, parathyroid hormone, calcitonin, etc.), cytokines (i.e., RANKL), and other compounds (i.e., growth factor, vitamin D, prostaglandin, etc.). Osteoblasts produce RANKL (receptor activator of nuclear factor kappaB ligand), a cytokine involved in differentiation, maturation, and activation of osteoclasts.

Table 18.2 Medications associated with bone loss or fractures

Glucocorticoids (>3 months cumulative dose in past year at prednisone dose of 7.5 mg or equivalent)
Anticonvulsants
Aromatase inhibitors
Antiandrogen therapy
Excess thyroid replacement
Anticoagulants (long-term heparin therapy)
Chemotherapy
Depo-medroxyprogesterone
Gonadotropin-releasing hormone (GnRH) agonists
Selective serotonin reuptake inhibitors
Proton pump inhibitors
Preformed retinol/vitamin A supplements >10,000 IU
Thiazolidinediones
Antiretrovirals (tenofovir, certain protease inhibitors)

RANKL binds to the receptor RANK found on the osteoclast surface to start the osteoclast differentiation, activation, and bone resorption process. Factors that affect this regulation can lead to an imbalance in normal bone physiology, such as loss of estrogen during menopause, aging, certain conditions, or medications.

Diagnosis

Identifying individuals at risk for further bone loss and fractures and targeting osteoporosis treatment to the individual patient is the key in preventing future fractures. Diagnosis of osteoporosis is established by fracture risk assessment, quantifying risk using validated 10-year fracture risk assessment tools such as CAROC or FRAX, and bone mineral density measurement with a dual-energy X-ray absorptiometry (DXA). Also, spinal X-rays may be warranted to check for vertebral fractures. Assessment for fracture risk should begin after the age of 50 years for both women and men, or younger if presence of secondary causes [6]. Osteoporosis is defined as a T-score of 2.5 or more standard deviations below the peak bone mass for young adults, and a T-score of −1 to −2.5 is considered osteopenia (low bone mass). However, treatment decisions should be guided based on 10-year fracture risk assessment and individual

patient characteristics (i.e., risk profile, other medical conditions, and preferences) [6].

Management

The goal of therapy is to prevent further bone loss and prevent future fractures. All patients should receive education on their fracture risk, treatment options including preventative measures and osteoporosis medications, and goals of therapy. The treatment plan should be individualized to the patient to ensure adherence.

Non-pharmacological Therapy

General preventative measures include calcium and vitamin D, exercise (includes weight bearing, resistance, and balance), smoking cessation, limiting caffeine intake to <400 mg daily (approximately four cups of coffee), and preventing falls. Osteoporosis Canada currently recommends 1200 mg of calcium (preferred dietary intake) and vitamin D 800–2000 IU daily [6]. Hip protectors have been shown to reduce hip fractures in patients in long-term care facilities [6]. Any secondary causes of osteoporosis should also be identified and treated before starting on osteoporosis treatment.

Pharmacological Options

There are a number of pharmacologic options to treat osteoporosis (Table 18.3). Most options available are antiresorptive agents including bisphosphonates (alendronate, risedronate, etidronate, zoledronic acid [ZA]), RANK-Ligand inhibitor (denosumab), selective estrogen modulator (raloxifene), and hormone therapy (HT). The only anabolic agent available in Canada is recombinant parathyroid hormone (teriparatide). All of these agents have evidence of vertebral fracture reduction, while a number also have non-vertebral and hip fracture reduction in randomized control trials (alendronate, risedronate, ZA, denosumab, teriparatide, and HT) [6]. Some studies have also shown a reduced mortality rates in patients at high risk of fractures. There are a range of formulations, routes of administration, and dosing regimens to choose from, allowing for individualization to enhance adherence. Osteoporosis Canada recommends the following as first-line therapies for preventing fractures:

Table 18.3 Classes of drugs used in the management of osteoporosis

Drug class	Drug	Dose
Antiresorptive agents		
Bisphosphonates	Alendronate	70 mg po once weekly[a] 10 mg po daily
	Risedronate	35 mg po once weekly[a] 5 mg po daily 150 mg po monthly
	Etidronate	Cyclic: 400 mg/day po × 14 days, then calcium carbonate (500 mg elemental) × 76 days
	Zoledronic acid	5 mg intravenous infusion once yearly
RANK ligand inhibitor	Denosumab	60 mg subcutaneous injection every 6 months
Selective estrogen receptor modulator	Raloxifene	60 mg po daily
Hormone therapy	Various estrogen products	Conjugated estrogen 0.3–0.625 mg daily, oral 17 beta-estradiol 0.5–1 mg, 25–50 μg patch Transdermal gel 1–2 pumps
Anabolic agent		
Recombinant parathyroid hormone	Teriparatide	20 μg subcutaneous daily

[a]Most common dose

- Postmenopausal women:
  - Vertebral, non-vertebral, and hip fractures: alendronate, risedronate, ZA, and denosumab. Hormone therapy can be considered if a woman also has vasomotor symptoms requiring treatment.
  - Vertebral fractures: raloxifene, etidronate can be considered if intolerant of first-line options
- Men: alendronate, risedronate, ZA, and denosumab
- Glucocorticoid-induced osteoporosis (on >3 months cumulative of prednisone or equivalent at 7.5 mg daily or higher): alendronate, risedronate, ZA, or denosumab

Pharmacologic therapy should be considered in all patients who are at high risk of fracture (>20% risk of fracturing in the next 10 years) or if they have experienced a fragility fracture after age 50. If using FRAX algorithm for assessing fracture risk, therapy should be considered if the patient has major fracture risk >20% or hip fracture risk of 3%. Initiating therapy in patients at moderate risk of fracturing (between 10% and 20% risk of fracturing) should be based on significant risk factors and patient preference. General preventative measures should be considered in patients at low risk of fracture (<10%), and no pharmacologic therapy is required.

Initial Assessment of a Patient

The initial assessment of patients diagnosed with osteoporosis and those people at risk of osteoporosis is similar. Pharmacists play an important role in the screening and management of these patients. Pharmacists are in an ideal position to screen patients who are at high risk for fractures and provide tailored patient education on osteoporosis risk factors, preventative measures, and medication options, as well as recommend follow-up with their primary care provider for bone mineral density testing [7]. Pharmacists can assess medication appropriateness for patients on osteoporosis medications by assessing drug interactions, medical contraindications, adverse reactions, and long-term risks with medications. Furthermore, they can monitor and support patients with adherence to osteoporosis medication or if experiencing adverse effects. As with any other chronic medical condition, initial assessment of patients begins with a collection of complete relevant history (demographics, history of present illness, medical history, social history, medications (prescription and non-prescription), social history, laboratory and physical exam findings). Additionally, fracture history, historical height loss, and history of falls should be collected.

- *Assessment of patient for fracture risk (not yet diagnosed with osteoporosis)*: All postmenopausal women and men over the age of 50 years should be screened for risk factors for bone loss or fractures. The purpose of risk factor assessment is to identify patients who may be at risk for fractures, as well as who should be assessed for bone mineral density with DXA. Risk factor assessment includes capturing all of the following information:
  - Personal fracture history – assess if fragility fracture (low vs. high trauma fractures); type of fracture to determine if related to osteoporosis
  - Medication history (focus on medications that are linked with bone loss or fractures such as glucocorticoids, aromatase inhibitors, anticonvulsants, diuretics, and others – see Table 18.2)
  - Family history of osteoporosis (parental history of hip fracture)
  - Smoking status, alcohol intake
  - Menstrual status in women (assess age of menopause to determine if early menopause or postmenopausal)
  - Medical conditions that may lead to bone loss or fractures (i.e., RA, hypogonadism, chronic renal failure, GI malabsorption [e.g., celiac, IBD], hyperparathyroidism, and others – see Table 18.1)
  - Assess for other potential causes of low bone mass (e.g., history of anorexia)

  Osteoporosis Canada recommendations for who should get a BMD include anyone over

the age of 65 years and postmenopausal women or men over the age of 50 years who have risk factors.

The two Fracture Risk Assessment tools used in Canada are the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) and Fracture Risk Assessment (FRAX) created by the World Health Organization. The CAROC uses BMD (femoral neck T-score), age, sex, fragility fracture, and glucocorticoid use to stratify patients into low (<10%), moderate (10–20%), and high (>20%) risk of fracturing within the next 10 years. FRAX also includes these risk factors but also captures BMI, family history (parenteral hip fracture), current smoker, alcohol intake, and secondary osteoporosis. The inclusion of BMD with the FRAX is optional.

- *Assessment of the appropriateness of the selected osteoporosis medication given the patient's future fracture risk*. Assessment of THE appropriateness of an osteoporosis medication involves an understanding of the patient's risk of fracturing within the next 10 years using a Fracture Risk Assessment Tools (either CAROC or FRAX), BMD results, history of fragility fractures, historical or prospective height loss, fall risk, and osteoporosis risk factors (medical conditions, medications that can lead to further bone loss). In some patients, especially if reported height loss or back pain, vertebral imaging may be required to diagnose vertebral fractures. Additionally, it requires an understanding of the evidence for fracture risk reduction (vertebral, hip, and non-vertebral fractures) for each of the pharmacologic options (see Table 18.3). Decisions on who to treat are as follows:

  High risk defined as CAROC >20% risk of fracturing in the next 10 years *or* if they have experienced a fragility fracture after age 50, FRAX major fracture risk >20%, or hip fracture risk of 3%:

  Pharmacologic therapy should be offered to all patients at high risk.

  Moderate risk defined as 10–20% risk of fracturing

  Pharmacologic therapy may be considered, but it is a clinical judgment decision and depends on if the patient has other significant risk factors for further bone loss or fractures – for example, if the patients have had fractures (e.g., vertebral fracture shown on spine X-ray or a wrist fracture), are on certain medications (e.g., glucocorticoids, aromatase inhibitors in women or androgen deprivation therapy in men), have conditions that can cause bone loss or fractures, or have fall risk.

  Low risk defined as <10% risk of fracturing

  No pharmacologic therapy is required. General preventative measures should be considered.

- *Assessment of the appropriateness of the selected osteoporosis medication given the patient's characteristics*. A detailed patient history, focusing on the clinical risk factors for bone loss or fractures, is important to identify future fracture risk as well as to help choose among the therapy options. In addition, risk factor for falls is important to capture, especially modifiable risk factors which can be addressed. Patient's preference for therapy, including routes of administration and dosing regimens (i.e., once weekly vs. every 6 months vs. once a year), should be considered. Comorbidities, concomitant medications, compliance issues, and drug coverage should be reviewed to rule out contraindications, potential drug interactions, and future adherence problems. Table 18.4 outlines patient-specific factors to consider when starting on specific osteoporosis medications.
- *Assessment of the appropriateness of the selected osteoporosis medication based on potential issues that may occur with each medication*. When initiating an osteoporosis medication, also consider the potential for adverse effects with specific agents in an individual patient, including long-term risks. For example, capturing swallowing difficulties or esophageal dysmotility in patients can help decide among the options (e.g., alendronate is associated with esophagitis). Bisphosphonates

Table 18.4 Patient considerations when initiating therapy

Medication	Factors to consider
Oral bisphosphonates	No issues swallowing or having medications get "stuck" in their throat Adequate renal function (calculated CrCl >30 mL/min) Need to space from all food and drinks (other than plain water) for 30 min after taking dose Previous major jaw surgery and/or jaw radiation (if yes, then should be avoided)
IV zoledronic acid	Adequate hydration prior to administration Adequate renal function (calculated CrCl >30 mL/min)
Denosumab	Willingness to have injections
Teriparatide	Willingness to inject on a daily basis Cost 2-year maximum lifetime usage
SERMs	No history of VTE
HT	No history of VTE

HT hormone therapy, *SERMs* selective estrogen receptor modulators, *VTE* venous thromboembolism

and denosumab have been associated with a risk of osteonecrosis of the jaw and atypical fractures with long-term use, though these events are extremely rare, it may be helpful to identify patients at increased risk such as patients with a history or major or planned dental surgery. Table 18.5 includes a list of adverse effects with osteoporosis medications.

Physical Assessment Skills

Physical assessment can be used to determine the extent of osteoporosis deformities (i.e., kyphosis), as well as assessing for vertebral fractures. The assessment of height loss and postural changes are important in the initial examination of a patient. Proper technique for measuring height is key; a wall-mounted stadiometer is preferred over other measurement devices. Patients should stand in their bare feet with heels touching the wall, as well as the back or buttocks, while

Table 18.5 List of most common drug complications in patients with osteoporosis

Drug	Common adverse reactions and laboratory monitoring/precautions	Red flag complications
Bisphosphonates (alendronate, risedronate, zoledronic acid)	Upper GI symptoms (monitor weight loss if severe GI symptoms) Muscle aches/pains Hypocalcemia – monitor calcium and albumin Infusion-related complications (only ZA) – flu-like symptoms, bone/muscle pain Renal toxicity (only ZA IV)	Atypical femoral fracture – sudden onset of thigh pain Osteonecrosis of the jaw – inform dentist prior to major dental work
Denosumab	Dermatologic reactions (eczema, rash) Muscle pain Theoretical risk of increase in infections	Atypical femoral fracture – sudden onset of thigh pain Osteonecrosis of the jaw – inform dentist prior to major dental work
Teriparatide	Orthostasis after injection – sit or lay down on first administration Leg cramps Headache, dizziness Hypercalcemia – monitor calcium and albumin	Theoretical risk of osteosarcoma
SERMs	Hot flushes, sweating Leg cramps Peripheral edema	VTE (increased risk in people with previous history of VTE)
HT	Breast tenderness Bloating, water retention Headache	VTE (increased risk in people with previous history of VTE)

HT hormone therapy, *SERMs* selective estrogen receptor modulators, *VTE* venous thromboembolism, *ZA* zoledronic acid

looking straight ahead with their chin horizontal to the ground. This measurement is sometimes difficult to do if a patient is significantly kyphotic, as they may not be able to get their back or buttocks to touch the wall. Measurement of height and height loss is a red flag for a potential vertebral fracture. Current height can be compared to the person's height at the age of 20; if there has been a 4 cm or greater loss of height, further investigation is warranted, such as a lumbar and thoracic spine X-ray to determine if there are vertebral fractures. If the patient is uncertain of their height at age 20, any recent documentation of height can be used; a loss of 2 cm or more would indicate further investigation is warranted.

For assessment of vertebral fractures, other physical exam techniques are included below:

- Occiput to wall distance can be measured as well. This is an indicator of potential thoracic vertebral fractures. Have the patient stand with their ankles and buttocks touching the wall, and keeping their chin horizontal, then have them try to touch the back of their head to the wall. Ideally, this distance should be 0 cm, but a distance of 5 cm or greater may indicate thoracic spine fractures.
- Rib–pelvis distance is another measure of kyphosis. Have the patient stand facing away from you with their arms outstretched. The space between the bottom of the ribs and the top of the pelvis should be at least two fingerbreadths apart.
- The spine can also be percussed by thumping a closed fist along the midline. This should be done relatively gently. Pain that is localized to the midline of the spine is also indicative of potential vertebral fractures.

To coincide with assessment of osteoporosis, assessment of falls can be useful in determining which patients are at increased risk of fracture. The most predictive factor for someone having a future fall is if they have had a fall in the past. Other risk factors include polypharmacy, certain medications (benzodiazepines, diuretics, psychotropics), use of a gait aid, and cognitive impairment. The Timed Up and Go (TUG) test is one quick and easy to administer assessment that can be used as a fall screen. To administer the TUG test: (1) have the person stand up from the chair, (2) walk 3 meters at normal pace, (3) turn, (4) walk back to the chair at normal pace, and (5) sit down again. If it takes the person more than 12 seconds to complete this test, they are considered at higher risk of a fall.

Follow-Up Assessments

Adherence

Bisphosphonates are generally associated with a high rate of non-compliance due to many factors such as: osteoporosis is a symptomless condition, administration and spacing of doses from other medications/food can be difficult to manage, and patients may not remember to take extended form dosing (i.e., once weekly). Compliance and appropriate administration (spacing of medications from food, etc.) of bisphosphonates should be reinforced at refills. Bisphosphonate compliance is improved with once weekly or once monthly dosing; however, rates still remain quite poor. For the medications administered less frequently, such as denosumab and zoledronic acid, patients may need reminders that a dose is due.

Control–Efficacy

Signs and Symptoms

In follow-up monitoring for osteoporosis, patients should be asked about any new fractures (i.e., while on therapy) or if they have new onset of back pain. Height should again be measured to determine if any height loss has occurred since the previous visit. Any new fractures since the last visit should be assessed, as well as a determination of whether the fracture was a fragility fracture. A fracture while on therapy, if the patient has been adherent, may be considered a failure to therapy. This may mean the patient requires a change in therapy. In addition, a reassessment of risk factors should occur, and a subsequent recalculation of FRAX and/or CAROC to deter-

mine if the patient's risk status has changed. An increase in risk may mean reassessment of therapy, for example, a decrease in fracture risk (moving from moderate to low) could mean therapy can be discontinued. Patients may lower their risk by quitting smoking, lowering alcohol intake, and being off corticosteroid therapy.

Laboratory

Renal function should be reassessed at follow-up as well, especially if the patient is at risk of poor renal clearance of bisphosphonates. Renal function should be calculated prior to a dose of zoledronic acid being administered as well. Other lab work such as calcium and albumin can be reviewed, but not necessarily needed if patient is doing well and has no other comorbidities. Markers of bone turnover (NTX, CTX) can be assessed in patients who are suspected of not adequately responding to antiresorptive therapy.

Imaging

In general, after the start of therapy, you can repeat a DXA in 1–3 years. For higher-risk patients, a DXA may be done after 1 year to ensure response is adequate and to determine if the BMD is dropping over time. A change in BMD can be reported with the diagnostic report, and this is most accurate if the patient continues to have their BMD measured with the same device; therefore, it is recommended when possible that patients have their follow-up DXA scans done at the same clinic as the previous scan. Thoracic and lumbar spine X-rays can be done at the same time as a follow-up DXA or if the patient develops new back pain as vertebral fractures can be silent and the patient may not have any symptoms.

Adverse Drug Reactions

As a key part of assessment, pharmacists should determine how patients are able to tolerate the medications prescribed for their osteoporosis. Adverse drug reactions or side effects can lead to non-compliance with medications and put the patient at risk of fractures. Table 18.5 shows some of the commonly occurring adverse reactions with osteoporotic medications as well as red-flag complications that occur rarely, but patients should be advised of when starting these medications.

Drug Holidays

There is controversy surrounding when to stop bisphosphonates in patients at mild to moderate risk of fracture. Long-term use of bisphosphonates is associated with a higher risk of atypical femoral fracture and osteonecrosis of the jaw, and as such, long-term therapy should be re-evaluated approximately 5 years after initiation of bisphosphonate therapy. In patients who are assessed to be at high risk for osteoporotic fracture, drug holidays should not be considered [8]. The evidence for drug holidays with denosumab is not as clear. Discontinuation of denosumab can lead to an abrupt decline in a patient's BMD and a potential increase in fracture risk. As such, drug holidays are generally not recommended with denosumab therapy. If a patient sustains an atypical femoral fracture while on either bisphosphonate or denosumab therapy, continued treatment with anabolic agents should be considered, dependent on their calculated fracture risk.

Disease Complications

The major complications related to osteoporosis are fractures. These fractures occur in bone that is primarily trabecular bone, such as the vertebrae and the hips. Once people suffer from one fragility fracture, they are at a much higher risk of future fractures – this is termed the fragility cascade; having one fracture predicts the chance of a person having a future fracture. If a patient suffers a fracture while on appropriate therapy, the first consideration is if the patient has been adherent. If they have not been adherent to therapy, a discussion of how to improve adherence would be beneficial or a consideration of changing therapy to something that is easier for the patient to manage should be discussed. For example,

patients who find it difficult to separate doses of oral bisphosphonates from other medications and/or food may find that IV zoledronic acid once a year is easier to manage. If the patient was adherent to oral bisphosphonate therapy, and spacing it appropriately from food and calcium, a change in therapy is likely warranted after a fragility fracture. Moving from a bisphosphonate to denosumab is definitely a consideration at this time. The use of teriparatide is limited mainly due to cost but can be considered in very fragile patients who consider to suffer fragility fractures while on bisphosphonate or denosumab therapy.

Clinical Pearls

- Assessment of people at risk of osteoporosis and those diagnosed with osteoporosis should include an assessment of risk factors, including medications that may contribute to bone loss and/or increase fracture risk.
- BMD is important both for initial diagnosis and assessment of risk.
- Vertebral fractures should be screened for at follow-up visits because patients may have one without knowing.
- Monitoring patients at follow-up should include an assessment of adverse effects from osteoporosis medications, as well as an adherence check.

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Rheumatoid Arthritis

19

Jill J. Hall and Jason Kielly

Chapter Objectives

1. Describe the epidemiology, etiology, clinical presentation, and diagnosis of rheumatoid arthritis.
2. Describe the goals of therapy and the management strategy for rheumatoid arthritis.
3. Conduct an initial assessment of a patient newly diagnosed with rheumatoid arthritis.
4. Conduct a follow-up assessment of a patient on disease-modifying antirheumatic drug therapy, considering the regimen's effectiveness and safety and the patient's ability to adhere.

Background

Epidemiology and Etiology

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation, pain, stiffness, and progressive joint destruction. RA is the most common inflammatory arthritis, affecting approximately 1 out of every 100 Canadians. It can occur at any age, with increasing prevalence between 40 and 60 years of age, and affects women two to three times more than men. Indigenous peoples are at a greater risk of developing RA and often have a more serious disease course [1].

The exact cause of autoimmune inflammation associated with RA is unknown; however, it is thought to result from a complex interaction between genetic and environmental risk factors. Cigarette smoking increases disease susceptibility and may increase risk of greater disease severity. Certain infections (viral and bacterial) have also been thought to trigger RA, but no single agent has proven to be responsible.

Pathophysiology

In RA the immune system can no longer differentiate self from non-self (foreign) tissues and attacks the synovial membrane, the layer of tissue that lines joints and secretes synovial fluid. The synovium becomes thickened and inflamed forming pannus (a layer of granulation tissue), which invades and destroys the cartilage and eventually the surface of the bone leading to joint destruction. While the factors that initiate the inflammatory response are unknown, the activation of T-cells and B-cells, along with the production of pro-inflammatory cytokines, leads to progressive

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bone breakdown and joint destruction. Some patients with RA form antibodies called rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA). RF is positive in 60–70% of patients with RA, and seropositive patients tend to have a more aggressive disease. High levels of ACPA are also indicative of aggressive disease and poorer outcomes; measurement is useful in the differential diagnosis of early polyarthritis, because of the relatively high specificity for RA.

Clinical Presentation

The symptoms and course of RA varies from patient to patient and is characterized by periods of flares and remissions varying in length and severity. The majority of patients develop symptoms gradually, with the predominant symptoms being joint pain, stiffness, and swelling. Morning stiffness greater than 1 hour is characteristic of RA. Typically, the metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP), and wrist joints are affected early in the disease; however, RA may affect almost any joint in the body with the exception of the thoracic and lumbar spine, the distal interphalangeal (DIP) joints, and the first carpometacarpal (CMC) joint.

Patients may present with or develop a number of extra-articular manifestations. Non-specific symptoms might include fatigue, weakness, and anorexia. A number of patients develop rheumatoid nodules (non-painful, pea to mothball size subcutaneous nodules on pressure points or in the lungs), pleuritis, pleural effusions, and vasculitis. Sjögren's syndrome associated with RA leads to a combination of dry eye (keratoconjunctivitis sicca) and dry mouth. Rheumatoid arthritis in association with splenomegaly and neutropenia is known as Felty's syndrome.

Patients may also have laboratory abnormalities. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), non-specific markers of inflammation, are commonly elevated and patients may experience anemia of chronic disease. When aspirated, synovial fluid is often thickened and cloudy. Erosions will be seen on radiographs at the first visit in 20% of patients and will be present in up to 70% of patients at 1 year if left untreated.

Table 19.1 Comparison of rheumatoid arthritis and osteoarthritis

Characteristic	Rheumatoid arthritis	Osteoarthritis
Joint pain	With activity and at rest	With activity
Joint symptoms	Pain, swelling, warmth, stiffness	Pain, bony enlargement
Joint pattern	Symmetric	Asymmetric
Morning stiffness	≥60 minutes	<30 minutes
Systemic symptoms	Common, especially fatigue	Absent
Acute phase reactants	CRP and ESR elevated	Normal

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate

Osteoarthritis and RA are the most common types of arthritic disorders, but they differ significantly in presentation (Table 19.1). Since management of the two conditions differs significantly, early evaluation and diagnosis are essential to optimize patient care.

Diagnosis

The diagnosis of RA should be considered in patients with persistent bilateral swelling or inflammatory pain in multiple joints. Criteria revised and developed in 2010 note a diagnosis of "definite RA" based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis better explaining the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from individual scores in four domains: number and site of involved joints (range 0–5), serological abnormality (range 0–3), elevated acute-phase response (range 0–1), and symptom duration (two levels; range 0–1) [2]. The new criteria are intended to help identify patients earlier in the course of disease so that treatment may be initiated as soon as possible. Where there is diagnostic doubt, x-ray, ultrasound, or magnetic resonance imag-

ing (MRI) can be used to improve the certainty above clinical criteria alone [3].

Prognosis

Clinical features associated with poor prognosis include early functional limitations, extra-articular disease, positive RF or ACPA, and early erosions on x-ray. However, clinical outcomes in RA have improved significantly with changes in drug therapy and treatment approach. Outcomes are dependent on a number of factors: degree of disease activity, pre-existing joint damage, psychological health, and comorbidities. Left untreated, inflammation and joint damage can readily lead to functional disability that can impact mobility and ability to work, resulting in significant financial and productivity losses, as well as emotional and social burdens affecting quality of life.

Patients with RA are at increased risk of serious comorbidities. Half of all deaths are cardiovascular related and patients with poor disease control are at increased risk of lymphoproliferative disorders (e.g., lymphoma, leukemia, and multiple myeloma) and lung cancer. Infections (especially upper and lower respiratory), osteoporosis, depression, and fibromyalgia also occur more frequently. To date, patients with RA have experienced reduced life expectancy and although recent Canadian evidence suggests that the risk of death in patients with RA is improving over time, it still remains elevated compared to the general population (40–50% more deaths) [4].

Management

Optimal management of RA requires rapid and sustained suppression of inflammation with immunomodulatory disease-modifying antirheumatic drugs (DMARDs). Evidence suggests that there is a "therapeutic window of opportunity" where the disease is more amenable to treatment, and aggressive therapy within this window can slow disease progression and long-term structural damage. RA patients treated with aggressive therapy within 3 months of symptom onset have better outcomes than patients treated later after symptom onset [5]. Tight control using a "treat to target" approach tailored to the disease activity of the individual patient and aimed at achieving remission is critical for optimizing long-term outcomes [6–8]. There are a number of treatment approaches aimed at achieving tight control (e.g., step-up, combination, step-down therapy), and the best approach is not clearly defined. What is important is frequent assessment of disease activity, usually every 3–6 months, with modification of DMARD therapy as necessary to achieve treatment goals. Determination of "response" and attainment of remission are measured using tools such as the Disease Activity Score (DAS-28), Simplified Disease Activity Index (SDAI), or Clinical Disease Activity Index (CDAI), all disease activity scores using a 28-joint physical exam, as well as the ACR-20 (American College of Rheumatology) that measures 20% improvement in various components. The DAS score is calculated using an ESR or CRP, while the SDAI and ACR-20 scores include a CRP (the CDAI does not include a laboratory marker). These scores are also used to determine eligibility for and ongoing reimbursement of the DMARD therapies used to treat RA by provincial and private drug benefit plans.

Non-pharmacological Therapy

A number of non-pharmacological measures play a role in the comprehensive management of RA in addition to drug therapy. All patients should receive education about their disease, treatment options, and goals of therapy. Helping patients and their families understand RA will empower them to take an active role in their care. Patients may also benefit from education programs, such as those offered by the Arthritis Society of Canada. Other non-pharmacological options include:

- Physical therapy
- Occupational therapy
- Weight reduction/nutritional therapy
- Emotional and psychological supports

Pharmacological Therapy

There are a number of medications available for RA treatment (Table 19.2). Methotrexate is the anchor drug in the treatment of RA and is the drug of first choice, given alone or as combination therapy. Ideally, methotrexate should be started within the first 3 months of symptom onset and rapidly titrated to 20–25 mg/week as tolerated, ideally by subcutaneous route [9]. Patients who have markers of a poorer prognosis, moderate-high disease activity, and recent onset of disease may be considered for initial combination DMARD therapy to increase the likelihood of attaining rapid, tight control of symptoms [6].

NSAIDs (e.g., naproxen 500 mg po BID) or corticosteroids (e.g., prednisone 20 mg po daily ×2 weeks, then tapered off over 6 weeks, or methylprednisolone 60 mg IM ×1) may be used as "bridging therapy" for symptomatic relief if

Table 19.2 Classes of disease-modifying antirheumatic drugs (DMARD) used in the management of rheumatoid arthritis

Drug class	Drug	Dose
Conventional synthetic DMARD		
	Hydroxychloroquine	200–400 mg daily po Maximum: 5 mg/kg ABW or 6.5 mg/kg/day IBW
	Leflunomide	10–20 mg daily po
	Methotrexate	*Initial*: 10–25 mg weekly po, subcut or IM (may increase by 5 mg q1–4 weeks to achieve maintenance dose) *Maintenance*: 15–25 mg weekly po, subcut or IM (single dose if tolerated or in two divided doses q12H) *For po doses > 15 mg, divided doses are better absorbed and tolerated*
	Sulfasalazine	*Initial*: 500 mg BID po and then increased to maintenance dose of 1 g BID po
Biologic DMARD		
B-cell depletors	Rituximab	1 g × 2 doses 2 weeks apart IV; infusions are given with 100 mg of methylprednisolone Doses can be repeated after 5–6 months
IL–6 inhibitors	Tocilizumab	Dosing for IV administration: 4 mg/kg q4weeks IV, infused over 1 hour; may increase to 8 mg/kg IV q4weeks if response is inadequate
		Dosing for subcut administration: 162 mg weekly For patients <100 kg start with 162 mg subcut every other week and increase to weekly based on response.
	Sarilumab	200 mg Q2weeks subcut
T-cell inhibitors	Abatacept	<60 kg: 500 mg IV initial infusion 60–100 kg: 750 mg IV initial infusion >100 kg: 1 g IV initial infusion After initial dosing, administer at 2 and 4 weeks, and monthly thereafter
		Dosing for subcut administration: 125 mg weekly starting within 24 hours of IV loading dose; the same weekly subcut dose is recommended even if IV loading dose is not provided
TNF-inhibitors	Adalimumab	40 mg q2weeks subcut
	Certolizumab	400 mg at weeks 0, 2, and 4 and then 200 mg q2weeks subcut. May give 400 mg q4weeks subcut as maintenance dose
	Etanercept	25 mg twice weekly or 50 mg once weekly subcut
	Golimumab	50 mg once monthly subcut 2 mg/kg IV at 0 and 4 weeks, then q8 weeks thereafter
	Infliximab	3 mg/kg IV at 0, 2, and 6 weeks, and q8 weeks thereafter For incomplete response, dose may be increased to 10 mg/kg and/or the frequency may be increased up to q4 weeks
Targeted synthetic DMARD		
JAK-inhibitor	Baricitinib	2 mg daily po
	Tofacitinib	5 mg BID po

ABW actual body weight, *BID* twice daily, *IBW* ideal body weight, *IL* interleukin, *IM* intramuscular, *IV* intravenous, *JAK* janus kinase, *po* oral, *subcut* subcutaneous, *TNF* tumor necrosis factor

needed. They provide quicker relief of symptoms compared with DMARDs, which take weeks to months to achieve maximal benefit. Short-term use of NSAIDs or high-dose corticosteroids can also be used to manage acute flares. However, it is important to note that NSAIDs have no impact on disease progression and corticosteroids are associated with a number of unwanted effects with long-term use.

A number of natural health products are thought to have anti-inflammatory effects and thus may be of benefit in the treatment of RA. Evidence suggests that omega-3 fatty acids (fish oils) (but not omega-6 or omega-9 fatty acids) may improve the symptoms of early RA and reduce the rate of DMARD failure [10]. Other agents, such as glucosamine and chondroitin, turmeric, and ginger, while generally well tolerated, lack evidence of benefit in RA. Patients who wish to try these agents should be encouraged to objectively monitor their symptoms and set a date to reassess effectiveness (e.g., 3 months), with discontinuation if there is no improvement. Products thought to boost the immune system (e.g., ginseng, echinacea, alfalfa sprouts) are not recommended as they may interfere with DMARD therapy. *Tripterygium wilfordii* products should not be recommended as use is associated with a number of severe side effects.

Initial Assessment of a Patient Newly Diagnosed with Rheumatoid Arthritis

Pharmacists can play an important role in the management of patients with RA, through assessment of medication appropriateness and patient education. They should assess the appropriateness of the initial DMARD regimen, along with any prescribed symptom management (or bridging) therapy, and are ideally positioned to support patient's adherence to therapy, including helping them navigate adverse effects and drug interactions. As with patients with other chronic medical conditions, initial assessment of patients newly diagnosed with RA should begin with the collection of relevant medical history data (history of present illness, medical history, allergies, medications (prescription and non-prescription), social history, laboratory and physical exam findings). Initial assessment should include the following considerations:

- *Assessment of the appropriateness of the prescribed DMARD regimen given the patient's presentation*: Understanding the patient's history (disease onset, pattern of clinical findings (signs and symptoms)) will help the pharmacist determine the appropriateness of the initial DMARD regimen, as well as response (effectiveness) at follow-up. There is no known "best" treatment regimen for RA; rather, any of the evidence-based treat-to-target strategies may be used, with patient reassessment every 3–6 months, with or without bridging therapy:
  - *Step Up*: initial monotherapy (methotrexate with dose optimization unless contraindicated), with further DMARD therapies added if necessary
  - *Combination*: initial combination of DMARD therapies (including methotrexate with dose optimization unless contraindicated, along with hydroxychloroquine and/or sulfasalazine,), with addition or replacement of a DMARD as necessary
  - *Step Down*: initial biologic DMARD (with methotrexate with dose optimization unless contraindicated) and/or prednisone, with the aim of discontinuing the biologic DMARD/prednisone once remission is achieved
- *Assessment of the appropriateness of the selected DMARD regimen given the patient's characteristics*: In addition to consideration of severity of illness, a patient's preferences with respect to route of administration and common adverse effects can often be taken into consideration along with comorbidities, allergies, concomitant medications, plans for pregnancy, and drug coverage. Table 19.3 outlines patient-specific factors that should be taken into consideration with individual DMARD therapies.
- *Assessment of the appropriateness of the dosage regimen of the selected DMARD regimen*:

Table 19.3 Summary of patient-specific factors that should be taken into consideration with individual DMARD therapies

DMARD	Patient factors to be considered
Conventional synthetic DMARDs	
Hydroxychloroquine	PMH: G6PD deficiency (contraindicated); risk of retinal toxicity increased with dose >5 mg/kg actual weight, renal impairment, pre-existing ocular disease, concomitant tamoxifen use (along with age >60, hepatic impairment) DI: additive hypoglycemia with antidiabetic agents SH: tobacco use reduces effectiveness Pregnancy/breastfeeding: considered safe
Leflunomide	PMH: Test for HBV, HCV (and HIV in high-risk individuals) prior to initiation DI: Lower dose (e.g., 20 mg every other day) when used in combination with methotrexate; cholestyramine utilized to eliminate leflunomide from biliary circulation SH: Excessive alcohol intake should be avoided; one to two drinks per week generally considered safe Pregnancy: Contraindicated, as it causes birth deformities in animals; no reported birth deformities in humans
Methotrexate	PMH: Caution in patients with renal impairment (contraindicated GFR <10 mL/min), chronic liver disease, pre-existing immunodeficiency or blood disorders (leukopenia, thrombocytopenia); test for HBV, HCV (and HIV in high-risk individuals) prior to initiation DI: Lower dose (e.g., 15 mg) when used in combination with leflunomide; concomitant use of NSAIDs, PPIs, penicillins generally considered SAFE; TMP/SMX should be avoided SH: Excessive alcohol intake should be avoided; one to two drinks per week generally considered safe Pregnancy: Can cause miscarriage or birth deformities (females must use effective birth control and discontinue ≥3 months prior to conception)
Sulfasalazine	PMH: G6PD deficiency (contraindicated) Allergies: Sulfonamide allergy (salicylate allergy can be desensitized to enable use) DI: Antibiotics may reduce the gut bacteria needed to cleave sulfapyridine (active drug) from 5-ASA, reducing effectiveness Pregnancy/breastfeeding: Considered safe
Biologic DMARDs	
All	PMH: Hepatitis B or C (unless receiving/received effective antiviral treatment), csDMARDs preferred if previous treated or untreated skin cancer (melanoma or non-melanoma), active infection DI: Use with any other bDMARD or tsDMARD Coverage: Expensive
B-cell depletor Rituximab	PMH: Preferred if history of treated lymphoproliferative disorder Allergies: Murine protein Pregnancy: Contraindicated
IL-6 inhibitors (sarilumab, tocilizumab)	PMH: Exposure to tuberculosis DI: Active inflammation (IL-6) downregulates CYP enzyme activity, thus IL-6 inhibition may lead to improved drug metabolism Pregnancy: Risk may outweigh benefit; no pattern of congenital anomalies or increased risk of spontaneous abortion seen in limited data to date
T-cell inhibitor Abatacept	PMH: COPD, exposure to tuberculosis Pregnancy: Risk may outweigh benefit; no pattern of congenital anomalies or increased risk of spontaneous abortion seen in limited data to date
TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab)	PMH: Heart failure (NYHA class III-IV), multiple sclerosis, untreated hepatitis C, exposure to tuberculosis, previously treated lymphoproliferative disorder (csDMARD, abatacept, tocilizumab preferred), serious infections (csDMARD, abatacept preferred) Allergies: Murine protein (infliximab) Pregnancy: Risk may outweigh benefit; no pattern of congenital anomalies or increased risk of spontaneous abortion seen in limited data to date; some providers consider certolizumab pegol and etanercept to be compatible with pregnancy
Targeted synthetic DMARD	
JAK inhibitors (baricitinib, tofacitinib)	PMH: Exposure to tuberculosis, untreated hepatitis B or C DI: Affected by strong CYP3A4 inhibitors and CYP 3A4/2C19 inhibitors Pregnancy: Contraindicated

DMARD disease-modifying antirheumatic drug, *DI* drug interaction, *IL-6* interleukin-6, *JAK* janus kinase, *NSAID* non-steroidal anti-inflammatory drug, *PMH* past medical history, *PPI* proton pump inhibitor, *SH* social history, *TMP/SMX* trimethoprim/sulfamethoxazole, *TNF* tumor necrosis factor

Generally, patients start at the target dose; however, some DMARDs are titrated to minimize adverse effects. One such example is sulfasalazine, which should be titrated over at least 1 month to avoid GI adverse effects. Although many rheumatologists initiate methotrexate at full dose (i.e., 25 mg weekly), others will titrate from as low as 7.5 mg weekly.

- *Assessment of the appropriateness of the bridging regimen*: Given the delayed onset of effectiveness of conventional synthetic DMARD (csDMARD) therapies, a full-dose NSAID or tapering dose of prednisone is commonly prescribed to improve patient's pain, inflammation, and function in the short term. The lowest possible dose and duration should be utilized.

Physical Assessment Skills

In specialized practice settings, pharmacists might perform the physical assessment skills necessary to utilize various validated disease activity scoring tools, such as the DAS28 using either CRP or ESR, CDAI, and SDAI. Each of these assessment tools incorporates a 28-joint count (including MCPs, PIPs, wrists, elbows, shoulders and knees) and a patient and provider global assessment of disease activity (e.g., "*Considering all of the ways your arthritis has affected you, how would you rate yourself on a scale of 0 to 10*"). It is important to note that this does not mean that the numerous additional joints that may be affected by RA are unimportant, and they should also be considered as part of a global functional assessment, with or without further physical exam.

Clinical examination is the foundation of RA management. Each joint is inspected for deformity, alignment, and swelling. Joint lines and presence of synovitis are assessed by palpation, along with an assessment of tenderness. Passive and active range of motion should also be assessed and can readily be done in the primary care setting. For example, the pharmacist could ask a patient to attempt to make a fist or perform a 'finger tuck' test; wrist, elbow, and knee flexion and extension; and shoulder elevation via flexion or abduction and internal and external rotation.

Follow-Up Assessments

Control

Signs and Symptoms

Although the general practice pharmacist may not have the training and experience necessary to complete a tender and swollen joint count assessment, they can and should assess signs and symptoms of patients with rheumatoid arthritis as part of their routine follow up, for example at medication refill encounters. The ultimate goal is remission, defined by ACR/EULAR as a tender and swollen joint count, CRP, and patient global assessment of ≤1 each [7]. Even without physical exam skills, pharmacists can ask key questions to determine the patient's response to therapy, targeting a lack of signs and symptoms of the disease. For example, "*Considering all of the ways your arthritis affects you, how do you feel your arthritis has been over the past week on a scale of 0 to 10*" could be used for someone still experiencing signs and symptoms. For someone who has low disease activity or who perhaps is more stoic, a question like "*Is there anything you're not doing right now because of your joints*" gives the clinician the opportunity to discuss patient goals and/or get a better sense of ongoing functional limitations.

Pharmacists practicing in primary care can also readily assess presence and duration of morning stiffness ("*When you wake up in the morning, are you more stiff than later in the day?*" And if so, "*How long does it last?*"), pain level ("*How would you rate your pain on a scale of 0 to 10, where 10 would mean that you could not get out of bed?*"), and range of motion (hands, wrists, shoulders) as previously outlined.

The Health Assessment Questionnaire Disability Index (HAQ) is a patient-reported measure of disease activity that provides information about a patient's functional status (basic activities of daily living). It includes 20 questions related to self-care (e.g., dressing,

hygiene, eating, gripping, and activities like errands or chores) that are rated with respect to difficulty in completing the specified task, along with notation of any aids/devices utilized or help from another person required. This tool is commonly utilized by rheumatologists but can be readily adopted by pharmacists in primary care to track improvement from DMARD therapy [11, 12].

If the patient's DMARD regimen (mono- or combination therapy) fails to achieve remission or low disease activity, then a change should be made, often with the addition of a disease-modifying therapy to a well-tolerated, partially effective regimen. Pharmacists may identify the ongoing use of an NSAID or cycling use of prednisone as a signal of a patient with uncontrolled disease; this is another opportunity to conduct a patient assessment and potentially intervene.

Laboratory

Markers of systemic inflammation, CRP and ESR, are also used to measure effectiveness of DMARD therapy and are part of the DAS28 and CDAI assessment tools. A CRP <10 mg/L is a requirement in the ACR/EULAR Boolean-based definition for remission [7, 13].

Diagnostic Imaging

Radiographs of the hands and feet are recommended as often as every 6–12 months in patients with recent onset, active disease and in whom bony erosion is suspected despite minimal physical findings or functional limitations [3, 6]. A change in therapy should be considered in patients with radiographic progression despite a reasonable clinical response. However, use of radiographs should be minimized in those with established disease and those in remission.

Other imaging modalities, such as ultrasound and MRI, can also be used to guide changes in DMARD therapy [3, 6]. Ultrasonography is particularly helpful to confirm clinical examination findings (whether synovitis is present) and to guide intraarticular corticosteroid injections, as it can be conducted in the clinic setting.

A lack of progression on radiographs of the hands and feet is also required for ongoing reimbursement of biologic (bDMARD) and targeted synthetic (tsDMARD) DMARD therapies by provincial and private drug benefit plans.

Adverse Drug Reactions

Pharmacists play an important role in monitoring how patients are responding to and tolerating drug therapy. Monitoring DMARD therapy involves inquiring about tolerance and adverse events, reviewing associated laboratory results, and reminding patients to contact a healthcare provider if there are concerns. Like all medications, treatments for RA carry risks of adverse events; however, the risk of joint damage and permanent disability from RA is much greater than the risk of severe side effects. The majority of side effects are uncommon, improve over time, and/or are reversible upon discontinuation. Table 19.4 summarizes the common adverse reactions and recommended lab monitoring, as well as rare but serious adverse events of currently available medications used to treat RA.

Patients with RA are at an increased risk of infections, particularly upper respiratory infections, and complications of those infections, due to the disease itself as well as the therapies used to manage it (bDMARDs and tsDMARDs more so than csDMARDs). In addition to recommendations for the general adult population, which include annual influenza vaccination, patients with RA should receive pneumococcal (conjugate followed at least 8 weeks later by polysaccharide) and herpes zoster (once ≥50 years) vaccinations [14]. Patients who are at high risk should also receive hepatitis B vaccine. These and other killed vaccines may be given prior to initiation of or during DMARD therapy, recognizing that the immune response may not be as pronounced or last as long on DMARD therapy. The exception is rituximab, which due to its mechanism of action, substantially reduces immunogenicity and vaccines

should be withheld for 6 months following its administration. Once bDMARD or tsDMARD therapy has been started, live vaccines are not recommended due to the risk of causing infections. Live vaccines should be administered at least 4 weeks prior to starting bDMARD or tsDMARD therapy. For more information on vaccine recommendations, see the Canadian Immunization Guide [14].

bDMARDs and tsDMARDs can also increase the risk of reactivation of latent tuberculosis infection (LTBI). Prior to starting therapy, patients will be screened for LTBI via skin testing and chest x-ray. Patients who screen positive will be required to take a 9-month course of isoniazid, initiated 1–3 months prior to starting the bDMARD or tsDMARD therapy.

Determining whether there is a risk of specific malignancies related to DMARD therapies remains an area of research; however, any risk must be balanced with the recognition that tight control of systemic inflammation also reduces the risk of RA-associated malignancies. Patients who have an active malignancy often have their DMARD therapy regimen adjusted, just as certain DMARDs are used preferentially in patients who have a history of various types of malignancy (see Table 19.3).

Complications

In addition to risk of infection and malignancy as outlined above, patients with RA are also at risk of:

Joint Deformity

Likely the most recognized complication of RA is joint deformity, which can lead to functional limitations and long-term disability.

CVD

RA and atherosclerosis both involve activation of T-cells, production of proinflammatory cytokines, and elevated CRP, thus it makes sense that the high systemic inflammatory burden of uncontrolled RA contributes to an increased risk of cardiovascular events and independently exacerbates modifiable risk factors like insulin resistance, dyslipidemia, and hypertension [15]. The best way to reduce cardiovascular risk in patients with RA is the achievement of tight control of both their arthritis (remission) and known modifiable risk factors (targets as outlined in guidelines). In addition, both MTX and TNFi have demonstrated benefit in reducing cardiovascular events in observational studies [16, 17].

Adherence

Patient adherence with their prescribed drug regimen is essential for tight control of the disease and symptom management and pharmacists play an important role in helping patients achieve optimal adherence. There are a number of factors that may affect medication adherence in RA. All patients should be counseled on the proper dosing schedule for each of their medications as a number of commonly used agents are not dosed daily (e.g., methotrexate, bDMARDs). When monitored properly, by clinical and laboratory assessment, the majority of side effects are rare and the most common ones improve over time and/or are reversible. Patients should be encouraged to complete their routine blood work and attend follow-up appointments with their rheumatologist even when they are feeling well. If a patient feels they are experiencing a side effect related to their medication, they should contact one of their healthcare providers to discuss the issue, as there may be strategies to reduce their burden. Medications used to treat RA can impair the body's ability to fight infections. Patients who have a fever, believe they have an infection, are having surgery, or have been prescribed an antibiotic should be counseled to contact their rheumatologist for instructions on how to manage their RA treatment. Finally, the majority of the bDMARDs and tsDMARDs are associated with significant costs; medication coverage issues

Table 19.4 Common and rare but serious adverse reactions and monitoring of DMARD therapy

Drug	Adverse reactions		Monitoring
	Common	Rare but serious	
Conventional synthetic DMARDs			
Hydroxychloroquine	GI (cramping, diarrhea), rash, headache, hyperpigmentation	Corneal and retinal deposition (higher risk with prolonged use of higher doses[a]); hypoglycemia	Baseline ophthalmologic exam then annually after 5 years[b] of treatment
Leflunomide	GI (diarrhea, nausea, decreased appetite/weight loss); less frequently rash, increased blood pressure, hair thinning/loss, increased LFTs	Bone marrow suppression, hepatic toxicity, pulmonary infection/fibrosis *Alcohol restriction may minimize hepatic toxicity*	Blood pressure, CBC, ALT, SCr, Plt, Alb q2–4 weeks for ≥3 months, then q2–3 months
Methotrexate	GI (nausea, diarrhea), feeling unwell/tired for 24–48 hours post dose; less frequently headache, hair thinning/loss, mouth sores/ulcers	Bone marrow suppression, hepatic toxicity, renal toxicity, pneumonitis *Alcohol restriction may minimize hepatic toxicity*	CBC, ALT, SCr, Plt, Alb q2–4 weeks for ≥3 months, then q2–3 months
Sulfasalazine	GI (nausea, cramping, diarrhea), rash, photosensitivity, headache	Bone marrow suppression	CBC, Plt, ALT q2–4 weeks for ≥3 months, then q3 months
Biologic DMARDs			
B-cell depletor (rituximab)	Infusion reactions[c] (flushing, itching, decreased blood pressure, etc.), CNS (fatigue, chills, headache), GI (nausea, cramping, diarrhea), rash	Bone marrow suppression, severe infusion reaction, PML, severe skin rash, bowel obstruction/ perforation, arrhythmias, renal toxicity	Baseline CBC, ALT, hepatitis B and C serology Repeat CBC and LFTs q2–4 months
IL-6 inhibitors (sarilumab, tocilizumab)	Injection site reactions (subcut administration), increased blood pressure, increased cholesterol	Infusion reactions (IV administration), bone marrow suppression, liver toxicity, renal toxicity, GI perforation, increased risk of malignancies,	Baseline CBC, ALT, SCr, lipid profile, hepatitis B and C serology, screen for latent TB Repeat CBC, ALT, SCr in 1–2 months then q3–6 months. Lipid profile in 1–2 months, then q6 months
T-cell inhibitor (abatacept)	Injection site reactions (subcut administration), headache, nausea, nasopharyngitis.	Infusion reactions (IV administration), exacerbation of COPD, increased risk of lymphoma, leukemia, and other malignancies	Baseline CBC, ALT, SCr, hepatitis B and C serology, screen for latent TB Repeat CBC, ALT, SCr in 1–2 months then q3–6 months
TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab)	Injection site reactions (SC administration), headache, nausea, rhinitis, cough	Infusion reactions (IV administration[c]), increased risk of lymphoma, leukemia and other malignancies	Baseline CBC, ALT, SCr, hepatitis B and C serology, screen for latent TB Repeat CBC, ALT, SCr in 1–2 months then q3–6 months

(continued)

Table 19.4 (continued)

Drug	Adverse reactions		Monitoring
	Common	Rare but serious	
Targeted synthetic DMARDs			
JAK inhibitors (baricitinib, tofacitinib)	GI (nausea, dyspepsia, diarrhea), headaches, increased blood pressure/heart rate, increased cholesterol	Bone marrow suppression, hepatic toxicity, renal toxicity, GI perforation, increased risk of lymphomas and other malignancies	Baseline CBC, ALT, SCr, lipid profile, hepatitis B and C serology, screen for latent TB. Repeat CBC, ALT, SCr in 1–2 months then q3–6 months. Lipid profile in 1–2 months, then q6 months

ABW actual body weight, *Alb* albumin, *ALT* alanine aminotransferase, *CBC* complete blood cell count, *CNS* central nervous system, *DMARDs* disease-modifying antirheumatic drugs, *GI* gastrointestinal, *IBW* ideal body weight, *IV* intravenous, *JAK* janus kinase, *Plt* platelets, *PML* progressive multifocal leukoencephalopathy, *SCr* serum creatinine, *subcut* subcutaneous, *TB* tuberculosis, *TNF* tumor necrosis factor

[a]Cumulative dose >1000 g, doses >5 mg/kg ABW – 6.5 mg/kg IBW, or 400 mg/day for >5–7 years

[b]Yearly if high risk (liver/kidney disease, obesity, >60 years old, pre-existing eye disease

[c]Pre-treatment: acetaminophen, diphenhydramine and IV methylprednisone

should be assessed and addressed to ensure optimal compliance.

Clinical Pearls

- Pharmacists can play an important role in the management of patients with rheumatoid arthritis.
- Initial assessment involves assessment of both the prescribed DMARD regimen, which should be targeting remission, and any necessary bridging therapy given the patient's clinical findings.
- Assessment at follow-up includes the patient's ability to adhere to therapy, objective measures of disease activity, and discussion of any adverse effects, along with monitoring laboratory measures of DMARD effectiveness and safety.

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Depression

20

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Chapter Objectives

1. Describe the disease burden, epidemiology, diagnosis, prognosis, and management of major depressive disorder and other depressive disorders.
2. Conduct initial assessment of patients who present with new diagnosis of depression or who are suspected of having depression but have not been formally diagnosed.
3. Outline monitoring parameters and follow-up plans for patients using pharmacological therapy to manage their depression.
4. Provide guidance to patients on how to manage partial/non-response or adverse effects of medications.

Background

Depression is one of the most common mental health conditions in North America, and affects individuals of all ages, from children to the very elderly. According to the 2010 Global Burden of Disease study [1], depression is the second most disabling medical condition worldwide and affects more than 350 million people. It is estimated that half of these people are not treated [2]. Although there has recently been more awareness around the importance of mental health, there has not been a significant change in the incidence of depression in the Canadian population. Between 2002 and 2012, the incidence dropped only 0.1%, from 4.8% to 4.7% [3]. Pharmacists are well equipped to both screen patients for the presence of depressive symptoms and monitor therapy to ensure that remission is being achieved while ensuring patients do not experience adverse effects.

The term "depression" encompasses several different disorders, but management is very similar between different subtypes. They differ in their duration, timing, and precipitating factors. This chapter will mostly focus on major depressive disorder (MDD) but will include pertinent details of other types when required. Some of the more common subtypes and specifiers include the following, which are described in the Diagnosis section [4]:

- Major depressive disorder
- Persistent depressive disorder (PDD)/dysthymia
- Premenstrual dysphoric disorder (PMDD)
- Peripartum depression
- Depression due to medication/other substance or medical condition
- Major depressive disorder with seasonal pattern

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Epidemiology and Burden of Illness

One out of every nine Canadians (11.3%) will experience major depression during their lifetime [3]. The annual prevalence in Canadians aged 15 and older is 4.7%, with women being affected almost twice as often as men (4.9% vs 2.8%). The pervasiveness varies between different age groups. Young adults aged 18–30 have very high rates of depression (12.4% in a 2002 Statistics Canada survey [5]). This may be due to the financial, academic, and social stressors that many young adults experience. Depression is also an important cause of disability in the elderly, with a 2010 meta-analysis indicating that the prevalence of depression is 7.2% in those older than 75. This meta-analysis contained data from Canada, the United States, and multiple European countries. Depressive conditions can become less common with aging, but it appears that in the very elderly it may be more prevalent than previously thought [6].

There is also a significant burden of illness in children, with 2.8% of those under 13 being affected and 5.7% of adolescents aged 13–18 [7]. In children, depression may contribute to behavioral challenges and impair normal psychosocial development. Depression in younger patients may become more difficult to treat the longer it continues and can persist into adulthood. Children who have depression are 4 times more likely to develop depression as an adult compared with those who do not.

The burden of a depressive disorder falls on the patient, their friends and family, and society as a whole. Depression has a major impact on physical, emotional, social, and functional status. The effects on mood can be obvious but can also lead to difficulty in interpersonal relationships, isolation from friends and family, and conflict with those around them. Patients also frequently experience bothersome physical symptoms. Many patients have impairment in their ability to work or attend school. This manifests as absences from work, missed classes, and decreased productivity when they are present. It is often made worse by the specific symptoms such as lack of motivation, cognitive dysfunction, fatigue, and insomnia. The average individual with MDD will have 34.4 days per year where they are unable to fulfill major roles [8] and experience a "healthy life expectancy" that is shortened by up to 6 years [9]. In 2001, Health Canada predicted that the financial burden of depression each year was $14.4 billion [10], which includes costs associated with treatment, loss of productivity, premature death, and medications. Given that the prevalence of depression in the overall population has not changed drastically since then, the current economic burden is likely similar, if not greater.

Etiology

The etiology of depressive disorders is unclear, and although there are some prevailing theories, they all have both supporting and contradicting evidence. More research is needed to determine the true cause of depression.

The monoamine theory was one of the early theories of depression and was proposed by a psychiatrist named Joseph Schildkraut in 1965 [11]. He concluded that depression came from a lack of monoamine neurotransmitters, specifically serotonin and norepinephrine. In animal and human studies, he observed that drugs such as monoamine oxidase inhibitors, which increased norepinephrine and serotonin, led to improved mood. Also, drugs such as reserpine, which inhibit these neurotransmitters, led to depressed mood [12]. However, there are some inconsistencies with this theory. In more targeted studies meant to support this hypothesis, results were inconsistent and the changes that were seen were not specific to depression over other mood disorders. Also, if it was a simple matter of replacing neurotransmitters, patients could expect immediate effect on taking their first antidepressant dose, when we know that it takes weeks to see benefits. In more recent studies on amine neurotransmitters, the role of dopamine has become a focus since its actions are so closely entangled with those of serotonin and norepinephrine. Many antidepressants have some effect on dopamine pathways [13].

Another theory concerns neuroendocrine mechanisms related to cortisol and impairment

in monoamine pathways. Depressive episodes are often preceded by stressful events, which the body responds to by producing cortisol. Persistent states of stress lead to desensitization of norepinephrine and serotonin receptors and dysregulation of the stress response [14]. Cortisol levels increase when serotonin and norepinephrine act on cells in the hypothalamus to release corticotrophin-releasing hormone (CRH) which starts the cascade that releases cortisol. When CRH was injected into the brains of experimental animals, they exhibited some of the common depressive symptoms seen in humans such as decreased energy, increased anxiety, and lack of appetite [12].

Recently, research has been focused on theories of trophic hormones and degeneration in the hippocampus as mechanisms that produce depressive conditions. Two substances being investigated are brain-derived neurotrophic factor (BDNF) and glutamate. BDNF levels are associated with mood: depressed patients have lowered levels, and those who are treated with antidepressants see recovery in their levels. Glutamate's proposed role is related to excitotoxicity and long-term potentiation of N-methyl D-aspartate (NMDA) receptors, but the exact mechanism is unclear. Neuroplasticity and neuronal regeneration theories are supported by scans of the brains of depressed patients that show loss of neurons and decreased levels of function in the hippocampus and prefrontal cortex. It is proposed that through the actions of serotonin, norepinephrine, and BDNF, antidepressants contribute to regrowth of neurons. This theory also aligns with the time course usually needed to see remission. It may also explain why some patients find exercise to be effective, because exercise is also thought to promote neurogenesis [12].

Risk Factors

The development of depression is complicated and related to genetic, environmental, and social factors. Although we cannot say for certain that a factor has caused depression in a patient, there are some risk factors that have been identified:

- Young adults and elderly
- Female gender
- Previous depressive episode or substance use disorder
- Family history of depression, suicide, or substance abuse
- Low socioeconomic status
- Use of certain medications and other substances (Table 20.1)
- Chronic medical conditions or disability (see Table 20.1)
- Stressful life events (see Table 20.1)

Table 20.1 Factors implicated in developing major depressive disorder

Drugs [13]	Medical conditions [18]	Social factors
Alcohol	Alzheimer's/dementia	Bereavement
Anticonvulsants	Cancer	Childhood abuse/neglect
Antirejection drugs	Chronic pain	Divorce
Beta-adrenergic blockers	Diabetes	Domestic violence
Clonidine	Heart disease/stroke	Environmental disasters
Corticosteroids	HIV	Identify as LGBTQ+[a]
Isotretinoin	Insomnia	Isolation
Nicotine/tobacco	Multiple sclerosis	Job loss
Oral contraceptives	Parkinson's disease	Social rejection
Substances/drugs of abuse	Spinal cord injury	Trauma
Tamoxifen	Traumatic brain injury	Unemployment
Varenicline	Withdrawal from substances	

This table does not include every drug or disease state that is associated with depression but covers the most significant contributors

[a]LGBTQ+, lesbian, gay, bisexual, transgender, queer, and other sexual/gender identities

- Presence of other psychiatric conditions, e.g., anxiety, substance use disorder
- Hormonal changes, e.g., peripartum, menopause, andropause

Presentation

As the most accessible health care providers, pharmacists are in an ideal position to recognize patients who may be experiencing symptoms of depression. Pharmacists might be the first persons to notice something as small as a previously very adherent patient no longer picking up medications, for example. Patient presentation can be highly varied and initial symptoms may be non-specific, so having a high index of suspicion is valuable. A depressed patient will not always complain of the typical "depressed mood and loss of interest in activities." Patients may mention fatigue, memory problems, stress, "mood swings," trouble with interpersonal relationships, or have a history of multiple medical visits with unclear symptoms and no real resolution [15]. Insomnia can be what causes many patients to first seek help, so it is important to probe those who are seeking over the counter sleep remedies for the presence of other symptoms. Box 20.1 presents some patients who would require further assessment for depression.

It is important to remember that not all patients will present with mood symptoms and may instead have physical complaints including vague aches and pains, gastrointestinal disturbances, weight changes, or headaches. When assessing patients with physical symptoms that do not have a clear cause, it is important to consider that they may indicate depression.

Children and adolescents tend to present with more behavioral problems, anxiety, irritability, somatic symptoms, phobias, and social withdrawal. As children and adolescents age, there is an increase in melancholy, psychosis, and suicidality [7]. Pharmacists may be able to intervene by guiding parents to access needed supports for their children and for themselves.

Box 20.1 Example Scenarios of Patients Who Would Require Further Assessment for Depression

1. AC is a 30-year-old man who was brought to the hospital after mentioning a suicide plan to his partner, who was very worried. His partner says that 3 months ago he lost his job, and so he spends his days "just sitting on the couch staring at the TV." He is often short-tempered and does not spend time with friends because it is "too much work." AC has also lost some weight but is not sure exactly how much; however, he says his clothes feel very loose.

2. ZT is a 16-year-old girl who comes to the pharmacy one day and asks what you suggest to help her sleep. She says she hasn't really slept well in about 3 weeks because she keeps waking up throughout the night. She reveals that she recently (~1 month ago) came out to her family as bisexual, and although her father is supportive, her mother has made many derogatory comments. When you ask further, she says she has been feeling "pretty down lately."

3. When you are filling a prescription for your patient LN, he mentions that he hopes he is "not like his mother" when he gets older because she is "cranky, never leaves the house, and stopped doing the things she used to love." He tells you that although she has been widowed for 20 years, she was not like this until 2 years ago when she moved to a seniors' apartment. Since then she has been difficult to be around and complains of constant aches and pains that won't go away no matter what she tries.

Diagnosis

Pharmacists are not usually responsible for making the official diagnosis of depression; however, it is important to be familiar with how a diagnosis is made and which other disorders should be

Table 20.2 Common symptoms in patients with depressive disorders

Psychological symptoms	Physical symptoms
Depressed mood	Insomnia
Loss of interest	Restlessness, agitation
Feeling overwhelmed	Weight gain or loss without trying
Feeling excessively guilty	Headaches, backaches
Anxiety	Vague aches and pains
Withdrawal from social life	Slowed movements or constant motion
Suicidal thoughts or actions	

Table 20.3 SADIFACES mnemonic for major depressive episode criteria [16]

S	Sleep – increased or decreased
A	Appetite – increased or decreased
D	**Depressed mood**
I	**Interest lost (anhedonia)**
F	Fatigue or decreased energy
A	Anxiety/agitation
C	Concentration difficulties
E	Esteem/excessive guilt or worthlessness
S	Suicidal thoughts or actions

"D" and "I" are bolded because at least one of the two is required, in addition to other symptoms, to diagnose depression

assessed for when a patient presents with symptoms related to depression.

Depression is characterized by a persistent depressed mood, and/or loss of interest in previously enjoyed activities, as well as other symptoms that are listed in Table 20.2. The diagnostic criteria for all depressive disorders are included in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V). It describes the symptoms, time frame, and other qualifiers that are needed for proper diagnosis.

Major Depressive Disorder

To be considered a major depressive disorder, five or more criteria must be present over a period of 2 weeks, with at least one of depressed mood or lack of interest. These symptoms are not related to a normal response to an event such as bereavement or a natural disaster, cause clinically significant distress or impairment in daily life, and are not due to another medical condition or to use of a substance. Also, the patient has never had a manic or hypomanic episode, and their symptoms are not better explained by another disorder [4]. The mnemonic SADIFACES [16] can help one remember the diagnostic criteria for a major depressive episode (Table 20.3). For further information, refer to the DSM-V.

Major depressive episodes (MDE) are classified based on severity. A *mild* MDE includes 5–6 symptoms, and the patient is usually still able to function relatively normally, although it may take more effort than usual. The symptoms themselves are often felt by the patient to be mild. A *moderate* episode usually involves 6–8 of the diagnostic criteria, and the patient may feel that the symptoms are of a medium level of severity and are having some impact on function. A *severe* episode includes all or almost all of the diagnostic criteria, severe enough to majorly affect the person's ability to function, or they are unable to function at all [16]. Some may also consider an episode to be severe any time there is suicidal ideation present.

Other Depressive Disorders

Dysthymia or persistent depressive disorder involves symptoms present for most of the day, almost every day for an extended period of time (1 year for children, 2 years for adults), and symptom-free periods that do not last more than 2 months. In addition to depressed mood, patients with dysthymia have 2+ of the MDD symptoms present, and those with persistent depressive disorder will meet the MDD criteria of 5+ symptoms [16].

Premenstrual dysphoric disorder (*PMDD*) is diagnosed when there is a pattern in multiple cycles where at least five of the symptoms are present in the week before menstruation starts, and they start to remit once it has started, and symptoms are absent in the week post-menses [4].

Peripartum depression is a major depressive episode that starts within 4 weeks of

delivery, but otherwise follows similar criteria to typical MDE.

Depression due to substance/medication includes the same features as MDD but is associated with taking or withdrawing from a substance and lasts beyond what is normally expected based on the pharmacology of the substance. The onset is within 1 month of taking a substance that could reasonably cause depression and the pattern does not better reflect another depressive disorder [4].

In *depression due to another medical condition*, the important qualifier is that the pathophysiology of the depressive symptoms is directly related to the medical condition, e.g., traumatic brain injury, stroke, or hypothyroidism. It can be very difficult to determine if the depressive episode is caused by the medical condition or if the medical condition is simply the stressor which precipitated a depressive episode [4].

MDD with Seasonal Pattern describes major depression which recurs and remits in a pattern with seasons. It is often present in the fall and winter, and then remits on its own in the spring and summer.

Depression Rating Scales

Several clinician and patient-rated scales have been validated in depression. They are useful in both diagnosis and follow-up of patients. Different scales have been developed for adults, elderly patients, and children [17]. The gold standard scales for adults include the HAM-D, BDI, and IDS/QIDS. For geriatric patients, the GDS is the preferred scale, and the CDRS-R is the most commonly used for children. Some of the more commonly used scales are available here:

- Hamilton Depression Rating Scale (HAM-D):
  - Scale: www.assessmentpsychology.com/HAM-D.pdf
  - Scoring: www.assessmentpsychology.com/HAM-D-scoring.pdf
- Beck Depression Inventory (BDI)
  - Scale: www.bmc.org/sites/default/files/For_Medical_Professionals/Pediatric_Resources/Pediatrics__MA_Center_for_Sudden_Infant_Death_Syndrome__SIDS_/Beck-Depression-Inventory-BDI.pdf
  - Online Test: http://treat-depression.com/depression-test
- Inventory of Depressive Symptomatology (IDS/QIDS)
  - Scale: www.ids-qids.org/download.html
  - Scoring: www.ids-qids.org/administration.html
- Zung Self-Rating Depression Scale
  - Scale and Scoring: www.outcometracker.org/library/SDS.pdf
- 9-Item Patient Health Questionnaire (PHQ-9)
  - Scale and Scoring: www.agencymeddirectors.wa.gov/files/AssessmentTools/14-PHQ-9%20overview.pdf
- Geriatric Depression Scale (GDS)
  - Scale and Scoring: https://web.stanford.edu/~yesavage/GDS.english.long.html
- Children's Depression Rating Scale Revised (CDRS-R)
  - Scale: www.opapc.com/uploads/documents/CDRS-R.pdf
  - Scoring: www.scalesandmeasures.net/files/files/Childrens%20Depression%20Rating%20Scale%20(1984).pdf
- Kutcher Adolescent Depression Scale (KADS)
  - Scale and Scoring: www.shared-care.ca/files/Kutcher_depression_scale_KADS11.pdf

These scales will be discussed further in the section on initial assessment.

Differential Diagnosis

Since there is a high rate of concurrent psychiatric disorders with depression, it is important to test for other disorders while assessing for depression. Other psychiatric disorders can also present very similarly to depression. Anxiety symptoms can be present in patients who have depression but may also be due to comorbid generalized anxiety disorder, obsessive-compulsive disorder, or another anxiety disorder. It would make sense to consider an anxiety disorder in a patient being treated for depression if all other symptoms responded to treatment, but symptoms of anxiety persisted.

Bipolar disorder should also be considered since these patients are often first treated when they present with a depressive episode. When given antidepressants, patients who have bipolar disorder often have a rapid switch to mania or hypomania, which can be very dangerous. Past episodes that resemble mania or hypomania should be enquired about to minimize the risk of this switch occurring. In addition to psychiatric causes, physical causes of symptoms should be considered. Anemia, dementia, and various endocrine conditions can produce depressive symptoms in some patients and should be ruled out with appropriate testing before diagnosing depression. Ruling out hypothyroidism is especially important because it often presents as depression but will remit once thyroid replacement therapy is started.

Investigations

Labs to be drawn to rule out physical causes.

- Thyroid-stimulating hormone (TSH) for hypothyroidism
- Complete blood count (CBC) for anemia
- Vitamin B12 level to assess for deficiency
- Cortisol levels (infrequently done)

Other investigations that may be done to confirm diagnosis of depression

- Mini-Mental State Evaluation to assess for dementia
- Psychologic rating scales for anxiety, other mood disorders
- Full medical history assessment to identify Parkinson's, stroke, or other disorders that directly cause depression
- Medication history, as well as use of any other non-prescription or recreational substances

Prognosis

Untreated episodes often last 6 months or longer, while on treatment the average time to remission is 20 weeks (4.6 months). Prognosis will vary based on the characteristics of the episode as well as patient adherence and response to treatment. Those who have better response to treatment generally have a lower risk of relapse and better prognosis than those who have more treatment-resistant depression [18]. In half of patients, their first episode will be their only episode. The other half of patients will have persistent (15%) or recurrent (35%) episodes. With pharmacotherapy, up to two-thirds of patients will eventually have remission of the episode, [19] but there is still a 30–40% chance of recurrence [20]. In children and adolescents who have one episode, the rate of relapse is as high as 70% [7]. Even once patients are in remission, 90% will experience some residual symptoms [20].

Management

Treating depression is important because although some episodes will remit on their own, the longer an episode continues untreated, the harder it will be to treat in the future (Fig. 20.1). Given the impact on quality of life and the higher risk of self-harm or suicide, it is preferable for patients with depressive disorders to be treated. Depression can be managed through both pharmacological and non-pharmacological means.

Short-term goals of therapy (acute phase of treatment) are focused on the current episode and usually include a time frame of 8–12 weeks or until remission is achieved. Main goals include:

- Alleviating symptoms
- Avoiding medication adverse effects
- Reaching remission

Long-term goals become the priority once remission is reached and they include:

- Maintaining remission, preventing relapse (continuation phase of treatment)
- Returning to full social, occupational, and interpersonal function
- Preventing recurrence (maintenance phase of treatment)

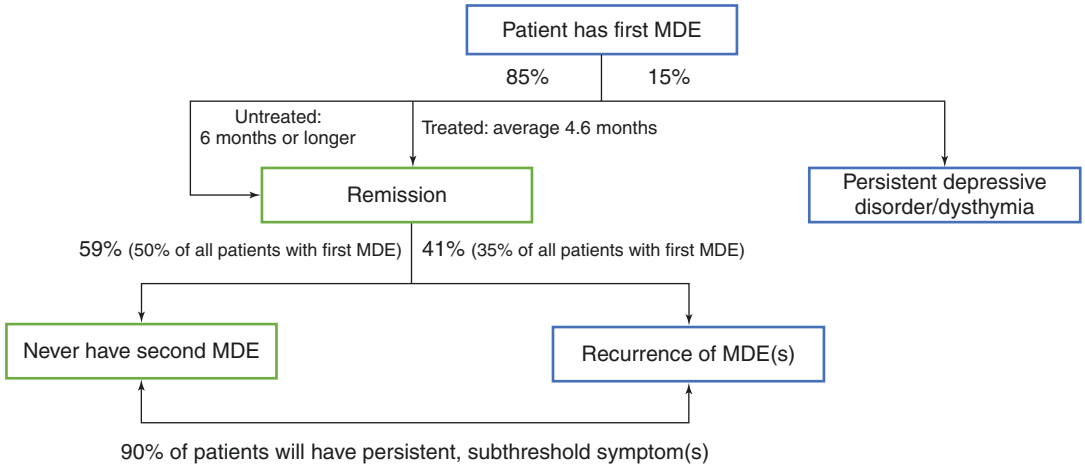


Fig. 20.1 Course of patients with a first major depressive episode. MDE major depressive episode as defined in the DSM-V. (Adapted from [18])

Non-pharmacological Therapy

Non-pharmacological treatment can be very effective in managing acute depressive episodes as well as providing patients with coping mechanisms to use in future episodes. Cognitive behavioral therapy and other forms of psychotherapy are at least as effective as pharmacotherapy for mild-moderate episodes [21]; however, the cost and time commitment may be prohibitive to patients. Light therapy has been found effective in mild-moderate depression, especially seasonal affective disorder. Exercise is also first line in mild depression, and a good adjunctive therapy in moderate-severe cases. Meditation and mindfulness-based practices can be used as adjuncts but are not recommended for sole treatment [22]. In more severe or resistant forms of depression, electroconvulsive therapy (ECT) and sleep deprivation can also be tried but come with greater risk to the patient. ECT is highly effective in patients who are willing to undergo the procedure or whose condition requires immediate intervention (e.g., extremely suicidal, psychotic, rapidly physically deteriorating), or those who do not want to be on pharmacotherapy [23].

As in most other medical conditions, patients use a variety of natural and alternative medicines including St. John's wort, omega-3 fatty acids, and S-adenosyl-L-methionine (SaMe). These three products have some weak evidence for efficacy in mild-moderate depression [22]. However, patients should be made aware of the comparative lack of regulation of these products and possibility of interactions with other medications. Products such as rose root, folate, DHEA, lavender, tryptophan, and many more have so far not shown efficacy.

Pharmacotherapy

Every patient will respond differently to different agents, so there is no designated drug to be used as the first choice every time like there may be in other conditions. It makes sense, then, to use the side effect and safety profile to guide the decision of which agent to use in a specific patient. This strategy may improve adherence, especially since patients tend to experience the side effects of a drug before the benefits [24]. The pharmacological treatments available in Canada are presented in Table 20.4. First-line treatments according to the Canadian Network of Mood and Anxiety Treatment (CANMAT) 2016 guidelines [25] include selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs) (excluding levomilnacip-

ran), bupropion, mirtazapine, and vortioxetine based on their efficacy and safety profiles. Other first-line agents that are not available in Canada include milnacipran, mianserin, and agomelatine. Selection of a specific agent depends on individual patient factors which will be discussed later. Older classes of medication such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are reserved for second- and third-line options because they tend to have a greater side effect burden for patients even though they have good efficacy. In treatment-resistant forms of depression, atypical antipsychotics and other medications can be used as adjuncts or after a patient has failed multiple usual antidepressants.

Duration of Treatment

For patients using pharmacotherapy, treatment should be continued for at least 6 months after remission and can be continued for up to 2 years or lifelong in those with high risk of recurrence

Table 20.4 Pharmacotherapy choices for depressive disorders

Class	Specific agents (usual adult dose)
Selective serotonin reuptake inhibitors (SSRI)	Citalopram (20–40 mg daily) Escitalopram (10–20 mg daily) Sertraline (100 mg daily bid) Paroxetine (20–40 mg daily, 12.5–25 mg CR daily) Fluoxetine (10–40 mg daily) Fluvoxamine (20–40 mg daily)
Serotonin/norepinephrine reuptake inhibitors (SNRI)	Venlafaxine (75–225 mg XR daily) Desvenlafaxine (50–100 mg daily) Duloxetine (30–60 mg daily) Levomilnacipran (40–120 mg daily)
Serotonin-2 antagonist/reuptake inhibitor (SARI)	Trazodone (150–400 mg daily in 1–3 divided doses with majority of dose at bedtime)
Serotonin-1A agonist/reuptake inhibitor	Vilazodone (20–40 mg daily with food)
Serotonin modulator and stimulator (SMS)	Vortioxetine (10–20 mg daily)
Noradrenergic/specific serotonergic agent (NaSSA)	Mirtazapine (15–30 mg qhs)
Norepinephrine/dopamine reuptake inhibitor (NDRI)	Bupropion (100–150 mg bid, 150–300 mg XL daily)
Tricyclic antidepressants (TCA)	Amitriptyline (75–200 mg daily) Nortriptyline (75–150 mg daily) Imipramine (75–200 mg daily) Clomipramine (75–200 mg daily) Desipramine (75–200 mg daily) Doxepin (75–200 mg daily) Trimipramine (75–200 mg daily)
Monoamine oxidase inhibitors (MAOI)	Phenelzine (15 mg bid-tid) Tranylcypromine (10 mg bid-tid)
Reversible inhibitor of monoamine oxidase-A (RIMA)	Moclobemide (150–300 mg bid)
Atypical antipsychotics	Aripiprazole (2–15 mg daily) Quetiapine (150–300 mg daily) Risperidone (1–3 mg daily) Brexpiprazole (1–3 mg daily) Olanzapine (2.5–10 mg daily) Ziprasidone (20–80 mg bid)
Other adjuncts	Buspirone (20–30 mg daily divided bid-tid) Lithium (600–900 mg daily, target serum level 0.6–1 mmol/L) Triiodothyronine (T3) (25–50 mcg daily)

Table 20.5 Factors to guide consideration of extended treatment [25]

Factors
Multiple, repetitive episodes
Unable to reach full remission on treatment, or have residual symptoms
Severe episodes, especially if suicidality, psychosis, major impact on function
Persistent depressive disorder or dysthymia
Other comorbid psychiatric condition or physical condition that contributes to symptoms
Continued emotional/psychological stressors, lack of social support

[25]. Patients who are at high risk of recurrence and will likely benefit from an extended duration of therapy are those who have one or more of the risk factors found in Table 20.5. The duration for non-pharmacological treatments is less clear, but often they can be decreased in frequency once remission is reached [22]. Interventions such as exercise do not have a defined duration but should be continued for their benefits to overall health.

Patients should be aware of the likely duration when therapy is started. Since the duration of maintenance therapy only starts once patients actually reach remission, the total length of treatment is usually not initially known. For example, Patient A may reach remission from their episode in 6 weeks, and Patient B may take 6 months. If both of these patients were unlikely to experience a relapse, they would both have 6 months of maintenance therapy, but Patient A would be treated for 7.5 months total and Patient B for 12 months. Also, since stopping therapy prematurely is associated with poorer outcomes, [18] patients should know that they should complete the full duration of maintenance therapy after remission is reached.

Initial Assessment of a Patient Newly Diagnosed with Depression

Once a patient is diagnosed with depression and presents to the pharmacy with a prescription for an antidepressant, pharmacists have an important role to play in ensuring that pharmacotherapy is optimized. After assessing the history of present illness, a careful assessment of their overall history must be done. This includes their full medical, medication, social, and family history, as well as assessing their allergies, functional status, medication adherence, and medication taking beliefs. Reviewing physical exam findings and any lab values or diagnostic imaging will ensure there are no other drug-related problems that need to be addressed. When gathering this information from patients, it should be done in a conversational manner that focuses on building rapport with the patient. Patients may be uncomfortable discussing their mental health and medical history, so pharmacists should offer to move the conversation to a more private location, especially if working in a busy community pharmacy.

Patient assessment should include the following areas, and information pertinent to depression should be clearly documented to facilitate future follow-up. By gathering this information, it allows you to determine the patient's baseline and any current risks, as well as ensuring that therapy is indicated, effective, safe, and that they can adhere to it.

Gather Information About Depression

Ask about specific symptoms, and what led the patient to seek treatment. This may reveal which symptoms are the most bothersome to the patient and help to guide therapy selection. Determine if this is their first episode or if they have had previous episodes. If there have been past episodes, ask about duration and management. Ask about functional impairment and if the patient has had to miss days of work or school, or has trouble taking care of themselves or their children. Exploring functional impairment may reveal specific patient goals for recovery. Depression rating scales can help to collect this information, as well as providing a method of monitoring improvement over time. Try to use the same scale for the same patient every time so you can track their progress. One easy way a self-rated scale could be integrated into community practice is when a patient drops off a new prescription or requests

a refill, they complete the scale while waiting for the prescription to be filled. Clinician rated scales may be more suited to primary care or appointment-based practice settings because of the time and training needed for proper administration. However, either type of scale can be used regardless of practice setting, and each has benefits and limitations (Table 20.6).

Suicide Risk

All patients with depression should be assessed for risk of suicide, homicide, and self-harm [13]. Some factors that should be considered when assessing the risk in a specific patient are included in Table 20.7. When approaching the subject of suicide with patients, the strength of the therapeu-

Table 20.6 Characteristics of common depression assessment scales

Scale	Scoring	Benefits	Limitations
HAM-D [17]	Clinician-rated Each item is scored from 0 to 4, then the points are totaled. Score of <7 indicates no depression, or remission if patient is on treatment. Mild depression is 7–17, moderate is 18–24, severe depression is >24 For the 21-item version, do not include items 18–21 in the score	Interview guide available, increases reliability High level of agreement between different reviewers and high test-retest reliability Widely used, most clinicians familiar	Some items include multiple concepts Does not assess atypical symptoms well Different symptom domains carry different weight (can overemphasize insomnia)
BDI [17]	Self-rated BDI-II is current version Each item scored from 0 to 3, points are totaled. Scores <11 indicate normal mood, 11–16 is mild mood disturbance, 17–20 is borderline depression, 21–30 is moderate depression, 31–40 is severe depression, and >40 is extreme depression	Measure current symptoms Does not require training to administer Patients can complete privately so may be more honest Aligns with DSM-V criteria	Patients must be able to understand the language it is written in Physical illnesses may artificially elevate score Length may be overwhelming to some patients
IDS/ QIDS [17]	Clinician-rated IDS-30 (30 items) and QIDS (16 items) Self-rated IDS-SR (30 items) and QIDS-SR (16 items) The scores are added up for each item according to the scoring guide. The guide and interpretation of scores for the different versions are found at: http://www.ids-qids.org	Better captures milder depression Includes atypical symptoms Each symptom domain has equal weight Items measure only one concept each	Scoring is complicated and requires scoring guide to do properly 30-item versions can take a long time to administer
Zung SDS [17]	Self-rated Each item scored 1–4, based on how often the item applies. For items 1, 3, 4, 7–10, 13, 15, and 19, a score of 1 indicates "a little of the time," and 4 indicates "most of the time." For items 2, 5, 6, 11, 12, 14, 16, 17, 18, and 20, the scoring is reversed with 1 applying to "most of the time" and 4 applying to "a little of the time." Scores of 50–69 indicate depression, and >70 is severe	Captures a broader variety of symptoms compared to BDI Moderate correlation with the HAM-D	Has not been revised since initial publication in 1965 so it is not often used clinically Does not indicate mild depression categories Minimal assessment of atypical symptoms
PHQ-9 [32]	Self-rated Questions 1, 2: one or both is rated as 2 or 3 Questions 1–9: at least 5 questions rated as 2 or 3; however, question 9 can be rated as 1, 2, or 3 Question 10: Rates as "somewhat," "very," or "extremely difficult" To calculate score, total up each column. Scores of 10–14 indicate mild depression, 15–20 moderately severe, and >20 as very severe	High sensitivity and specificity for diagnosing major depression Quickly rated and scored Includes patient's view on level of impairment Provides treatment recommendations based on score	To score properly, need to have the appropriate forms with the correct format Does not include physical symptoms, anxiety

(continued)

Table 20.6 (continued)

Scale	Scoring	Benefits	Limitations
GDS [33]	Clinician-rated or self-rated Answers associated with depression are "yes" to items 2–4, 6, 8, 10–14, 16–18, 20, 22–26, and 28 and "no" to 1, 5, 7, 9, 15, 19, 21, 27, 29, and 30 For each answer that matches the previous answers, 1 point Scores 0–9 indicate no depression, 10–19 mild, 20–30 severe	Yes/no format is easily understood Uses items that are phrased to be acceptable in elderly patients Distinguishes non-depressed, mildly, severely depressed patients	Questions about somatic symptoms correlated poorly with total score so not included Not yet commonly used in trials so may be hard to compare trials with GDS scores
CDRS-R [34]	Clinician-rated Items scored from 1 to 6 or 1 to 7 and scores from each question added up Scores 28 or less indicate remission or no depression, while scores >40 indicate depression	Combination of reports from child, observer, parents, school, and others Good at detecting response to treatment	May take a long time to administer Requires training to properly administer
KADS [35]	Self-rated 11-item version has better sensitivity than other versions Each item rated 0–3 and score totaled; however, total score does not correspond to diagnostic categories and is meant to be a measure of tracking symptoms in a specific patient	Uses language that is familiar to adolescents Correlates well with clinician assessment of severity Good sensitivity to change	Has not been directly correlated with other scales No validated diagnostic categories associated with score, so cannot be used to diagnose

HAM-D Hamilton Depression Rating Scale, *BDI* Beck Depression Inventory, *IDS/QIDS* Inventory of Depressive Symptomatology/Quick Inventory of Depressive Symptomatology, *Zung SDS* Zung Self-report Depression Scale, *PHQ-9* 9-item Patient Health Questionnaire, *GDS* Geriatric Depression Scale, *CDRS-R* Children's Depression Rating Scale Revised, *KADS* Kutcher Adolescent Depression Scale

Table 20.7 Factors that increase suicide risk [3]

Factors	
Age	*Comorbidities*
Older males	Concurrent substance abuse
Adolescents	Other mental health condition, especially personality disorders
Social or environmental factors	Chronic pain
Higher degree of isolation, hopelessness, loneliness	Cancer
Lack of support network	Psychotic symptoms, anxiety
Family history of suicide	Traumatic events and/or post-traumatic stress disorder
High degree of impulsiveness	Past suicide attempts or self-harm

tic relationship is essential: if a patient trusts you to have their best interests in mind, they may be more willing to tell you about suicidal thoughts. When patients do report suicidal ideation, the priority is keeping the patient safe. Questions that help to quickly identify patients who need immediate intervention include:

Do you have a specific plan?
Do you have the materials to carry out that plan?
If you leave here/go home, will you be safe?

Resources for patients who report suicidal ideation are available in the form of crisis phone lines, online, mental health professionals, and emergency rooms when needed. These resources will differ based on your location, so pharmacists should be aware of local resources and have contact information on hand to provide to patients.

A pharmacy-specific consideration for patients who report suicidal ideation is the supply of medication to provide. In a patient that you are concerned about, it might be appropriate to only provide a 1-week supply of medication at a time, or even dispense daily if you believe they are especially high risk. It may also guide the choice of therapy based on how great of a risk intentional overdose would pose. For example,

an overdose of amitriptyline is much more likely to be fatal than one with citalopram [26].

Consider Patient Medical and Medication History

The goal of collecting this information is to ensure that there are not medical conditions or medications the patient is taking that may interfere with, or be affected by, their antidepressant. Also, if a patient has responded well to an antidepressant in the past, they may respond well to that same agent again. Antidepressants have the potential for many drug interactions, so knowing a patient's full medication list is important. Some of the common interactions are listed in Table 20.8. Look for medical conditions and medications that may contribute to depression (refer to Table 20.1), as well as those that are contraindications to certain medications (Table 20.9). One consideration that is

Table 20.8 Summary of drug interactions for antidepressant classes [26]

Class	Interactions
All antidepressants	*Serotonin syndrome* MAOIs, linezolid, methylene blue (contrast medium), triptans, and many others Lithium and tryptophan may enhance serotonergic effects *St. John's wort* Herbal product that acts on serotonin, monoamine oxidase, and other targets to produce antidepressant effects Can cause serotonin syndrome, also has many interactions via liver microsomal enzymes Should not be used in combination with antidepressant drugs *Antiplatelet/anticoagulants/nonsteroidal anti-inflammatory drugs* Serotonin has an effect on platelet aggregation so increased bleeding risk with these combinations
Selective serotonin reuptake inhibitors (SSRI) Citalopram Escitalopram Sertraline Paroxetine Fluoxetine Fluvoxamine	*Cytochrome P450 liver microsomal enzymes* Many interactions since SSRIs are both substrates and inhibitors; check interaction reference every time Fluvoxamine and fluoxetine higher risk Paroxetine inhibition of 2D6 can have major consequences on drugs activated by it (e.g., tamoxifen, codeine) *Anticholinergic drugs* Paroxetine is highest risk *Additive sedation* Paroxetine and fluvoxamine highest risk *QT interval prolonging agents* Citalopram and escitalopram highest risk
Serotonin/ norepinephrine reuptake inhibitors (SNRI) Venlafaxine Desvenlafaxine Duloxetine Levomilnacipran	*Cytochrome P450 liver microsomal enzymes* Substrates and inhibitors of CYP isoforms, including 3A4, 2D6, and 1A2 Check drug interactions reference when combining with inducers, inhibitors, other substrates *Drugs with sympathomimetic effects* Increase heart rate and blood pressure
Serotonin-2 antagonist/ reuptake inhibitor (SARI) Trazodone	*QT prolonging agents* *Inducers of CYP450 2D6 and 3A4* *Induces metabolism of p-glycoprotein substrates* *Additive sedation* CNS depressants *Anticholinergics* *Taking with food increases extent of absorption but decreases peak concentration and slows onset*

(continued)

Table 20.8 (continued)

Class	Interactions
Serotonin-1A agonist/ reuptake inhibitor Vilazodone	*Cytochrome P450 liver microsomal enzymes* Substrate of 3A4 (major), 2C19 and 2D6 (minor) Moderate inhibitor of 2C19 and 2D6 Maximum dose 20 mg if strong 3A4 inhibitor present *Slight inhibition of p-glycoprotein, monitor drugs with narrow therapeutic range (*e.g.*, digoxin)* *Food increases absorption by about 50% so vilazodone should be taken with food*
Serotonin modulator and stimulator (SMS) Vortioxetine	*Cytochrome P450 liver microsomal enzymes* Metabolized by 2D6 and many other isoenzymes but does not induce or inhibit them Reduce dose by half if strong 2D6 inhibitor started
Noradrenergic/specific serotonergic agent (NaSSA) Mirtazapine	*Cytochrome P450 liver microsomal enzymes* Substrate of 2D6 and 3A4 *Enhances anticoagulant effect of warfarin, could be clinically significant in some patients* *Additive impairment with agents that cause sedation or motor impairment (ex: alcohol, benzodiazepines)*
Norepinephrine/dopamine reuptake inhibitor (NDRI) Bupropion	*Cytochrome P450 liver microsomal enzymes* Substrate of 2B6 Inhibitor of 2D6 Metabolism induced by HIV protease inhibitors *Avoid combination with other drugs that predispose patients to seizures (ex: steroids, antipsychotics, tramadol, alcohol)*
Tricyclic antidepressants (TCA) Amitriptyline Nortriptyline Imipramine Clomipramine Desipramine Doxepin Trimipramine	*Cytochrome P450 liver microsomal enzymes* Substrates of 2D6, 1A2, 2C19, and others Inhibitors of 2D6 Clomipramine interaction with grapefruit juice *Can exaggerate vasopressor response (ex: epinephrine)* *Agents that prolong QT interval* *Anticholinergic agents* *Additive sedation and CNS depression (*e.g.*, alcohol, opioids, benzodiazepines)* *Dopaminergic effects exaggerated with dopamine increasing agents*
Monoamine oxidase inhibitors (MAOI) Phenelzine Tranylcypromine	Numerous severe interactions with other medications and food, check product monograph and drug interaction resource every time and provide patient with a list of medications and foods to avoid
Reversible inhibitor of monoamine oxidase A (RIMA) Moclobemide	*Cytochrome P450 liver microsomal enzymes* Substrate and inhibitor of 2C19 and 2D6 *Anticholinergic agents* *Hypertensive effects with alpha/beta-agonists, amphetamines, buspirone, methylphenidate*

often not assessed initially is the patient's risk of QTc interval prolongation. In patients who are at high risk (elderly, females, electrolyte abnormalities, recent myocardial infarction, use of other QTc prolonging agents, congenital long QTc) and are starting on antidepressants known to prolong QTc interval (i.e., citalopram and escitalopram), an ECG should be done at baseline.

Pregnancy and Breastfeeding

There is little evidence for most antidepressants in pregnancy. The most clinical experience and evidence exists for SSRI's, so they are often chosen if a drug must be started. The evidence that exists does indicate some level of risk, but it needs to be balanced against that of untreated depression in the mother [27]. In patients already using antidepressants who become pregnant, the

Table 20.9 Patient-specific factors to guide selection of antidepressant drugs [26, 29]

Class	Absolute contraindications	Relative contraindications/ cautions	Other patient factors to consider
All classes of antidepressants	Combination with MAOI Patient with bipolar depression and no additional mood-stabilizing therapy Prior allergic reaction to that medication	Pregnancy and breastfeeding Renal or hepatic impairment Seizure disorder or history	Comorbid conditions Risk in overdose Financial burden and drug coverage
Selective serotonin reuptake inhibitors (SSRI) Citalopram Escitalopram Sertraline Paroxetine Fluoxetine Fluvoxamine	Class: Use within 2 weeks of MAOI (5 weeks if fluoxetine) Citalopram and escitalopram: Known or congenital QT prolongation Paroxetine: pregnancy	Class: Bleeding disorders Severe liver dysfunction Diabetes Citalopram and escitalopram: Use of other QT-prolonging agents; max dose 20 mg (cit) or 10 mg (escit) Paroxetine: Elderly	Class: Indicated for anxiety disorders Safer in overdose compared to TCAs Citalopram, escitalopram, fluoxetine, fluvoxamine: Health Canada approved for use in patients <18
Serotonin/ norepinephrine reuptake inhibitors (SNRI) Venlafaxine Desvenlafaxine Duloxetine Levomilnacipran	Desvenlafaxine Gastrointestinal narrowing/strictures, conditions that affect GI transit Duloxetine: Severe/end-stage renal impairment Uncontrolled glaucoma Levomilnacipran: History of stroke, cardiovascular disease Past cardiac intervention NYHA Class III or IV heart failure	Class: Bleeding disorders Hypertension Diabetes Venlafaxine: Poor adherence Desvenlafaxine: Cardiovascular, cerebrovascular conditions Lipid disorders	Desvenlafaxine, Levomilnacipran: Cost is important to consider, as they are more expensive than other agents Duloxetine: Indicated for chronic and neuropathic pain Levomilnacipran Not first-line based on less data about preventing relapse
Serotonin-2 antagonist/ reuptake inhibitor (SARI) Trazodone	Men: other risk factors for priapism (e.g., sickle cell disease)	Elderly patients Orthostatic hypotension Recent myocardial infarction	Insomnia in combination with other antidepressants or alone Manage "sundowning" in dementia
Serotonin-1A agonist/ reuptake inhibitor Vilazodone		Cardiovascular disease Hypertension Patient at risk of arrhythmia	Expensive, consider cost
Serotonin modulator and stimulator (SMS) Vortioxetine	Use within 2 weeks of MAOI or MAOI within 3 weeks of vortioxetine	Severe hepatic impairment	Expensive, consider cost
Noradrenergic/ specific serotonergic agent (NaSSA) Mirtazapine		Past myocardial infarction or angina History of stroke Prostatic hypertrophy	Sedation can benefit insomnia Helpful in patients who will not eat because stimulates appetite Weight gain can be significant

(continued)

Table 20.9 (continued)

Class	Absolute contraindications	Relative contraindications/ cautions	Other patient factors to consider
Norepinephrine/ dopamine reuptake inhibitor (NDRI) Bupropion	Current or past seizure disorder Patients undergoing withdrawal from alcohol or benzodiazepines Current or past bulimia or anorexia	Insomnia Anxiety Alcohol consumption Patients who have weight loss as a symptom Doses >150 mg daily in severe renal or hepatic impairment	Indicated for smoking cessation (brand: Zyban) More activating so beneficial in patients who are fatigued
Tricyclic antidepressants (TCA) Amitriptyline Nortriptyline Imipramine Clomipramine Desipramine Doxepin Trimipramine	Recent myocardial infarction Cross-reactivity within class for hypersensitivity reactions Patients at high risk of overdose	Any personal or family cardiovascular history Elderly Prostatic hyperplasia Glaucoma Thyroid dysfunction	Class: Benefit in neuropathic pain Doxepin Insomnia Amitriptyline, nortriptyline: Migraine prophylaxis
Monoamine oxidase inhibitors (MAOI) Phenelzine Tranylcypromine	Use of other serotonergic drugs within 2 weeks (3 weeks for vortioxetine, 5 weeks for fluoxetine) Cerebrovascular or cardiovascular disorders Recurrent or frequent headaches Liver damage Blood dyscrasias Pheochromocytoma Tyramine-containing foods: Check reference	Any foods that are not clearly fresh and free from preservatives can present a risk, even if stored properly in a refrigerator Hypertension Overdose can be fatal	May have better response in catatonic or treatment resistant patients
Reversible inhibitor of monoamine oxidase A (RIMA) Moclobemide	Use of meperidine	Renal impairment Overdose can be fatal	Avoids the dietary restrictions of irreversible MAOIs

decision is made based on a discussion between the mother and clinician.

Consider Appropriate Dose

Many antidepressants, such as SSRIs, are started at half of the therapeutic dose to make sure the patient will tolerate it, and then increased after a week. For other agents like bupropion, the starting dose may be therapeutic. Since many are metabolized by the liver, it is important to check for dosing adjustments that need to be made in cases of liver damage. This applies to most SNRIs, vilazodone, bupropion, and more. Kidney function can also guide dose and is important to consider for all agents but particularly paroxetine, SNRIs, TCAs, and mirtazapine. Some antidepressants will also have maximum doses based on age or comorbidities. For example, the maximum dose of citalopram in hepatic impairment is 20 mg/day, even though the usual maximum is 40 mg/day. Recommended dosing in common comorbidities can be found in individual drug monographs.

Consider Social and Family History

Assess the use of alcohol, caffeine, marijuana, and other recreational drugs. These substances may produce symptoms of depression or be used

by patients to alleviate symptoms. Withdrawing from substances may also play a role. Ask about the patient's occupation, family life, financial situation, overall lifestyle, and any major stressors that exist for them. These factors can help in assessing appropriateness of therapy and their ability to adhere to medication. Patients who have a first-degree relative with depression or other mood disorders are more likely to have depression themselves [28]. Patients may also respond to the same medications that family members have responded to. A family history of other mood disorders can also provide alternate diagnoses to consider if symptoms that are not congruent with depression are present.

Consider Barriers to Adherence

Antidepressant adherence is notoriously poor. One in five patients will not be adherent to their antidepressant prescription [25]. By addressing factors of intentional and non-intentional non-adherence early on, many of them can be mitigated. Practically, consider if patients can actually take the medication. Certain medications, like fluoxetine and escitalopram, come in liquid or orally dissolvable forms to assist patients who cannot swallow pills. Also, many of the newer agents are very expensive compared to equally effective older agents. For example, citalopram and vortioxetine are both first-line agents, but based on Canadian pricing, citalopram would cost a patient around $15/month, while vortioxetine would be closer to $100/month [29]. Depressive symptoms may present their own barriers in terms of low motivation or cognitive impairment. Psychological factors also need to be considered. Patients may think that medication is taking the easy way out or that they are "not really sick." There is also the misconception that antidepressants are "addicting." This needs to be addressed by pharmacists, and the difference between physical dependence and addiction explained in a way the patient can understand. Patients also should be aware that therapy can be slowly stopped once remission is maintained for an adequate length of time.

Physical Exam and Labs/Diagnostic Imaging

These investigations are usually done by the patient's physician in the process of diagnosis and available on request. In addition to confirming the diagnosis of depression, baseline information is needed when patients are started on medication to monitor for adverse effects. Specific values that should be noted at initial assessment are thyroid-stimulating hormone (TSH), a complete blood count (CBC) and vitamin B12, liver enzymes (LFTs), and serum creatinine (SCr). Weight should also be documented, especially if starting on antidepressants associated with weight gain or loss. If baseline lab values are not available, pharmacists should ensure they are ordered in a timely manner.

Follow-Up Assessment

The style of follow-up assessments may vary based on the practice setting and can be done over the phone or via in-person visits. When a patient is newly started on treatment, they should be followed up with at least every 2 weeks, if not weekly, to check for tolerance and early response, as well as any adverse effects. Once they are stabilized on therapy, follow-up intervals can be extended to every month or even every 3 months if they are in the maintenance phase of treatment.

Adherence

Medication adherence is very important with antidepressants. Patients should be advised not to discontinue their treatment without consulting their psychiatrist or other original prescribers. Even if patients have achieved remission, they should continue their treatment for the entire duration of therapy because patients who discontinue treatment early have overall worse prognosis and higher likelihood of relapse [30]. When asking about adherence, it is important to do so in a non-judgmental way that invites the patient to tell you about their concerns, instead of making

them feel like they are in trouble for not taking their medication perfectly. Pharmacists should work with patients at each encounter to maximize their ability to take their medication through identifying barriers and helping the patient to find solutions. Adherence aids such as pill boxes and reminders can be helpful for patients who have trouble remembering to take their medication. Pharmacists should also ask if any medication side effects are contributing to non-adherence.

Control

The goal of treating a depressive episode is to have a patient reach full remission. This is defined as no longer meeting diagnostic criteria for the depressive disorder, and a return to their normal level of functioning. This definition does include the possibility of some lingering symptoms, which many patients will have. Patients may not reach remission with one antidepressant, and in fact only about 1/3 will achieve remission with the first agent tried [19]. Most patients will take 6–8 weeks to reach remission once they are taking a therapeutic dose [25].

Response is defined as at least a 50% improvement on the score of a rating scale. This is why a baseline score is important and why the same scale should be used for the same patient each time. Partial response is defined as between 25% and 50% decrease in the score, while non-response is less than 25% change [30].

In the first 2–4 weeks of therapy, patients may have an early response (indicated by a 20% reduction in their symptom score [25]), and this is a positive predictor of reaching full remission with the agent they are on. The first symptoms that patients will notice changes in are often appetite, sleep, and motivation. Not having this early response does not mean they cannot respond, but if by 4 weeks they have seen no improvement, there is less chance of remission occurring with that particular agent [30]. Increasing the dose can also be tried if early response is not seen and the drug is being tolerated well.

Repetition of depression scales is the most common way to assess control of depressive symptoms. Since most scales consider symptoms over the past 1–2 weeks, they should ideally be assessed every 2 weeks. Pharmacists may not be seeing the patient that often, but scales should be administered as often as is practical based on your setting, and the scores recorded in a care plan. Although blood drug levels can be drawn, it is not recommended because it does not change management in most cases. It could be useful in a minority of patients if there are questions of adherence or suspicion that they are ultra-rapid or slow metabolizers [25]. There are no lab parameters that correlate well with efficacy of antidepressant therapy.

Even though remission/responses are defined numerically, also consider the patient and the specific goals that were set at the start of therapy. Ask about their progress toward these goals, especially if there were functional or symptom-related goals that they wanted to achieve. Even if they have reached the definition of remission on paper, if there is a bothersome residual symptom, it should be addressed. For some symptoms like insomnia, consider that they may indicate comorbid disorders.

For patients who do not reach remission Since many patients will not reach remission with the first medication, having a plan on how to address lack of response is a good idea. It will depend on the patient's preference and the factors indicated in Table 20.10 as to how to handle the situation. The two main options are switching to a different antidepressant or adding on another therapy. These could be atypical antipsychotics or other classes that have shown benefit in treatment-resistant cases. Some of the options for first-line adjunct therapy are listed in Table 20.4. Before making any changes to antidepressant therapy, always ensure you have assessed adherence and that the trial was an adequate dose and duration. Some patients may have depression that is more difficult to treat. Although there is not an official set of diagnostic criteria for "treatment resistant depression," the CANMAT guidelines suggest using inadequate response to adequate trials of two or more agents [25] as the cutoff to guide escalation of treatment. This means that the

Table 20.10 Factors to consider when deciding whether to switch or add therapy [25]

Favors switching	Favors adding
First antidepressant trial	2+ failed trials
Poorly tolerating current antidepressant	Low potential for interactions
High potential for drug interactions	Patient can manage added pill burden
High pill burden	Targeting specific symptoms (ex: insomnia)
No response (<25%)	At least partial response (25–50%)
Less urgent need for control (no suicidality or severe functional impairment)	Need for control is more urgent
	Previous poor tolerance of discontinuation syndrome

patient has not reached full remission, but they may still have had some degree of improvement. In more treatment-resistant patients, adjuncts may be more beneficial than switching because you will not lose the benefit from the current agent.

Strategies for switching agents When patients are switching antidepressants for any reason, pharmacists are responsible for helping them through the process safely. It is important to consider the nature of the agents that are being used. If switching between different agents in the same class, often you can immediately replace one with a full therapeutic dose of the other because their similar mechanisms of action will minimize the risk of discontinuation syndrome, e.g., citalopram to sertraline and venlafaxine to desvenlafaxine. The patient should still be aware that some withdrawal symptoms are possible. Another strategy is to cross taper the medications, which means that the new medication is started at the lowest available dose while still on the old medication and titrated up to the lowest therapeutic dose. Then, the old drug is tapered down slowly. This can be beneficial for patients who have more severe depression because it does not leave them with a "drug-free interval." However, it can potentially lead to increased side effects while both medications are being used. This should never be done with MAOIs, as the risk of adverse effects is too high. When you are concerned about combining the agents, as with MAOIs, a washout period is necessary. When switching to or from MAOIs or moclobemide, the usual washout period is 2 weeks. There are exceptions (e.g., 5 weeks for fluoxetine to MAOI), so the monographs of both drugs should be checked every time.

An excellent resource that can guide switching antidepressants is www.SwitchRx.ca, and it can also be used to create tapering schedules if discontinuing an antidepressant altogether.

Adverse Reactions

Patients should be asked about any side effects they have noticed since starting their antidepressant medications. When assessing an adverse effect that is thought to be related to a drug, ensure that the time course makes sense. Good examples are sexual dysfunction or insomnia, as both can be symptoms of depression, but could also be adverse effects of medication. Having a list of other medications they are taking will also help to identify if reactions are related to a drug interaction. It is important for pharmacists to ask about specific side effects because patients may not attribute a side effect to the medication or may not report it unless asked directly.

Some adverse reactions are common across all classes of antidepressants, while others may be class-specific. Since all current antidepressants have some role in increasing serotonin, associated adverse effects are possible for all classes. Bupropion tends to have less serotonergic effect than other antidepressants, so it may have lower rates of serotonergic side effects.

Some common adverse reactions are presented in Table 20.11, as well as those that are rare but severe enough that patients should be aware. A complete list of all adverse effects associated with each drug may be found in the individual monographs.

Discontinuation syndrome This can occur with all antidepressants but SSRIs and SNRIs are espe-

Table 20.11 Selected adverse effects of different antidepressants [13, 26, 29]

Drug or class	Adverse effect	Level of concern	Notes
All antidepressants	Serotonin syndrome	Rare but serious, requires referral	Usually occurs when multiple serotonergic medications are combined, or an overdose; rapid onset within 24 hours Symptoms: changes in mental status, diarrhea, hyperreflexia, agitation, tremor, seizures, arrhythmias, rhabdomyolysis, disseminated intravascular coagulation, respiratory arrest
	Suicidal ideation, behavioral disturbances	Rare but serious, requires referral	More common in adolescents/young adults More common in first few weeks of therapy Associated with agitation, akathisia, emotional lability, aggression, depersonalization Monitoring: Pharmacist to ask every 2 weeks until stable, then monthly
	Manic switch	Quite common, can be serious and requires referral	Occurs in patients with bipolar disorder only treated with antidepressants, or patients misdiagnosed with depression instead of bipolar disorder.
	Increased bleeding risk	Common, clinical significance varies	Concern when patient is also using anticoagulants, antiplatelets, or nonsteroidal anti-inflammatory drugs Ranges from mild bruising to severe bleeds Monitoring: bleeding/bruising drug interactions
	Sexual dysfunction	Very common, may be mild or serious impairment	Patients rarely report without being asked Lower rate with mirtazapine, bupropion, moclobemide Common reason for non-adherence Monitoring: Pharmacist to ask, as patients rarely self-report
	Acute angle-closure glaucoma	Rare but serious, requires referral	Medical emergency, risk of permanent vision loss Symptoms: Rapid onset of severe pain in the eye(s), blurred vision, redness Patients who already have elevated intraocular pressure or narrow ocular angles are at higher risk
	Increased risk of fractures	Uncommon but can be serious	Especially in patients who are using antidepressants for long-term treatment Dizziness/drowsiness can contribute to fall risk and fractures
All SSRI's	Nausea, headache, anxiety, drowsiness, dizziness, sweating, tremor, insomnia	Common, usually mild	Tend to remit with continued therapy, approximately 2 weeks Usually can be alleviated with non-pharmacological methods or changing administration time
	Weight gain/ loss	Uncommon, usually minor	Most SSRIs are weight-neutral; however, paroxetine associated with weight gain, fluoxetine with anorexia and weight loss Weight gain can be related to recovery of appetite when treatment is started
	Hyponatremia	Uncommon, can be serious and requires referral	Related to SIADH: syndrome of inappropriate antidiuretic hormone More common in elderly Symptoms: nausea, vomiting, confusion, muscle cramps/ weakness, seizure Monitoring: Na + level at baseline and if symptomatic
Citalopram, escitalopram	QT prolongation	Common, clinical significance varies	QT prolongation is common and dose related, unless elderly/other risk factors, arrhythmia and sudden cardiac death very rare Symptoms: palpitations, feeling faint/dizzy Monitoring: K+ and Mg2+, high-risk patients ECG done at baseline and if symptomatic

Table 20.11 (continued)

Drug or class	Adverse effect	Level of concern	Notes
Fluoxetine	Stimulating	Common, mild	Most stimulating SSRI
Fluvoxamine	Nausea, sedation, constipation	Common, can be more significant	Worse initially, and should decrease within approximately 2 weeks
Sertraline	Sexual dysfunction, diarrhea	Common, can be more significant	Highest rate among SSRIs Diarrhea often remits in about 2 weeks but sexual dysfunction does not
Paroxetine	Anticholinergic: dry mouth, dizziness, urinary retention, constipation, blurred vision	Common, can be more significant	Highest rate of all SSRIs Controlled release form might have less noticeable or less severe adverse effects than immediate release for some patients [36]
All SNRI	Same as SSRI class effects	Common, usually mild	Usually resolve in first 2 weeks of therapy
	Elevate blood pressure and heart rate	Common, usually mild	Tends to be sustained for duration of therapy Palpitations can also occur Monitoring: baseline blood pressure and heart rate, patient to check regularly
	Dry mouth	Common, usually mild	Dose-related, may be worse with venlafaxine and duloxetine
	Nausea and GI upset	Common, can be significant	Starting at low dose and titrating up slowly will decrease, and it usually remits within 2 weeks of reaching therapeutic dose Less frequent with desvenlafaxine
Venlafaxine, Des-venlafaxine	Elevated LDL, triglycerides, liver function tests	Relatively common, usually not significant	Monitoring: baseline lipid panel and liver function tests, repeat yearly unless symptomatic or other risk factors present
Duloxetine	Elevated liver function tests	Uncommon and usually minor	Monitoring: Baseline liver function tests, repeat if symptomatic
Levomilnacipran	Hyperhidrosis	Common, mild-moderate	Patient to report if bothersome, may be managed with non-pharmacological methods
	Erectile dysfunction and urinary hesitancy	Uncommon but may be significant	Dose-related
Trazodone	Priapism	Rare but serious, requires referral	Medical emergency and may lead to permanent impotence if not treated
	Orthostatic hypotension	Quite common, can be significant	Higher risk in elderly patients, can lead to falls
	Anticholinergic effects	Quite common, can be significant	Dose-related, elderly patients more sensitive
	Sedation	Common, significant impairment	Should be taken at bedtime based on degree of sedation May affect ability to drive or operate machinery safely
	QT prolongation	Uncommon, clinical significance varies	Arrhythmia and sudden cardiac death very rare, but should avoid using soon after cardiac event Symptoms: palpitations, feeling faint/dizzy Monitoring: K+ and Mg2+, high-risk patients ECG done at baseline and if symptomatic

(continued)

Table 20.11 (continued)

Drug or class	Adverse effect	Level of concern	Notes
Vilazodone	Nausea, vomiting, diarrhea	Common, usually mild	Usually occurs during initial treatment period and titration and remits within 1–2 weeks
	Weight gain	Common, usually mild	Approximately 1–2 kg increase in body weight over 1 year of treatment
	Muscle spasm	Common, usually mild	Few patients in trials discontinued the medication due to muscle spasm
Vortioxetine	Hypertension	Uncommon, little clinical significance	More significant increases in blood pressure (2–5 mmHg systolic) in the first 14 days of treatment but returned to normal with longer term use Monitoring: baseline blood pressure and patient to check regularly
	SSRI-like side effects	Uncommon, usually mild	Nausea comparable to SSRIs, but otherwise much lower incidence of adverse effects including sexual dysfunction, sedation, insomnia
Mirtazapine	Weight gain	Common, significant	Many patients gain greater than 7% of their current body weight Monitoring: body weight at baseline and regularly
	Sedation	Common, moderately significant	More common at lower doses because at higher doses, noradrenergic effect counteracts sedation May impact ability to drive or operate machinery
Bupropion	Insomnia, agitation, tachycardia, diaphoresis	Common, moderately significant	Administering in the morning minimizes effect of insomnia Monitoring: heart rate, sleep
	Seizures	Uncommon but serious	Dose related, see monograph for more information Monitoring: electrolyte abnormalities increase seizure risk
	Weight loss	Common, may be significant	May also be associated with decreased appetite Risk in patients with eating disorders like anorexia/bulimia
All TCAs	Anticholinergic effects	Common, can be significant	High risk in elderly patients – question indication Interactions with other medications that have same effect will be additive
	Antihistamine: weight gain, dizziness, drowsiness	Common, can be significant	Weight gain may affect adherence significantly Drowsiness/dizziness can affect ability to drive or operate machinery Monitoring: baseline weight
	Cardiotoxicity: arrhythmias, orthostatic hypotension	Common, may be clinically significant	At normal doses as well as overdose Contributes to lethality of overdoses
All MAOIs, RIMA	Hypertensive crisis	Common, usually severe, requires referral	Higher risk with irreversible inhibitors but still possible with RIMA Be very careful with drug interactions

SSRI selective serotonin reuptake inhibitor, *SNRI* serotonin norepinephrine reuptake inhibitor, *GI* gastrointestinal, *K+* potassium, *Mg2+* magnesium, *TCA* tricyclic antidepressant, *MAOI* monoamine oxidase inhibitor, *RIMA* reversible inhibitor of monoamine oxidase-A

cially implicated. Agents with shorter half-lives such as paroxetine, venlafaxine, and duloxetine are usually associated with worse symptoms, and need to be tapered more slowly [29]. Symptoms are usually not severe but, in some cases, may be disabling and can last 1–3 weeks. If patients stop their antidepressant abruptly, they are at risk of experiencing discontinuation syndrome, and patients who miss doses may also experience a milder form. The general symptoms include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances including shock-like sensations, and hyperactivity

and can be remembered using the acronym "FINISH." Even in patients who are tapered slowly, some symptoms can occur. One strategy to ease the process of discontinuation is to provide the patient with a single dose of fluoxetine, as its long half-life causes it to essentially taper itself off over the course of 3–5 weeks. If symptoms are severe, the original antidepressant can be restarted to alleviate symptoms and discontinuation can be retried later if the patient is willing [26].

Complications of Disease

There are several complications associated with depression. The first, and often most serious, is the increased risk of suicide. Patients with depression have a risk that is four times higher than that of the general population for adults [31], and seven times higher for children and adolescents [7]. Depression is also associated with cardiovascular disease, stroke, pregnancy complications, falls in elderly patients, and poor recovery after surgery.

Children of parents with poorly managed depression may have their cognitive and interpersonal development affected, and can experience problems with emotional regulation, internalizing, and attachment disorders. They are also at a higher risk of developing depression themselves.

Many patients who experience one depressive episode will also experience relapse or recurrence at some point in their life. This may be symptoms, a full major depressive episode or even persistent depressive disorder. Relapse is often defined by symptoms presenting again while treatment is ongoing but the patient has reached remission. Recurrence is usually after the patient has been asymptomatic for a longer period and then experiences another episode [30]. These terms are often used interchangeably.

Clinical Pearls

- Pharmacists are in a perfect position to screen patients for depression. Having a strong therapeutic relationship with patients will encourage them to report distress to you.
- Stigma plays a big role in the number of patients who are unwilling to seek help for depression and other mental illnesses. Be a non-judgmental resource for your patients who may be experiencing depression.
- Talk to every patient with depression (and their family if possible) about suicide risk.
- Involving the patient in decisions about management will increase their satisfaction with therapy and their adherence.
- Symptoms of depression are not a normal part of aging and should not be ignored in the elderly.
- Many patient and clinician resources for depression exist. Some of them are listed here.
  - Patients:
    - Canadian Mental Health Association: www.cmha.ca
    - Depression and Bipolar Support Alliance: www.dbsalliance.ca
    - Mood Fx: www.moodfx.ca/
    - Depression Hurts: http://depression-hurts.ca/en/default.aspx
  - Clinicians:
    - Canadian Network for Mood and Anxiety Treatment: www.canmat.org
    - Medication Info Share: http://medicationinfoshare.com/
    - Switch Rx: www.switchrx.ca
    - American Psychiatric Association: www.psychiatry.org

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Chronic Non-cancer Pain

21

Patrick R. Mayo and Sheila Walter

Chapter Objectives

1. To identify key features of chronic non-cancer pain as a pathological form of pain
2. To review assessment strategies that allow the clinical pharmacist to assess pain and evidence of reduced coping in chronic pain patients
3. To link pain and coping assessments to pharmacotherapy optimization and management

Background

In 1931, physician, theologian, philosopher, and missionary Albert Schweitzer opined that "Pain is a more terrible lord of mankind than even death itself." A study of the global burden of disease in 2010 reported that the prevalence rate for chronic pain comprised of low back pain and neck pain of 14.1% or that 964,094,000 people were living with chronic pain. Calculating the years living with disability (YLDs) from 1990 to 2010, it was discovered that there had been a 42.4% increase in YLDs over that time period, suggesting an increase in chronic pain. Low back pain alone contributed 10.7% to the total worldwide total of YLDs.

Chronic pain also demonstrates an age-related trend with the prevalence increasing through adult life, reaching a peak around the seventh decade [1]. The classical definition of pain as recommended by the International Association of Pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [2]. However, this definition does not accurately describe chronic pain, as chronic pain is not simply the sustained activation of acute pain pathways. In addition, there is enormous heterogeneity observed in chronic painful syndromes, so the term chronic pain has little diagnostic value and even less value for the determination of pharmacotherapy. A detailed taxonomy of non-cancer-related pain syndromes with specific treatment recommendations is beyond the scope of this chapter. However, within the confines of chronic non-cancer pain (CNCP), fundamental pain assessment and pharmacotherapy recommendations can be provided for clinical pharmacists as part of their ongoing assessment of pain pharmacotherapy. As patients have greater access to pharmacists, good pain assessment information can be vital for pharmacotherapy monitoring and for a critical assessment alerting the

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patient and the patient's primary care or pain physician of developments that may require implementing changes to both drug and non-drug therapy. The current opioid crisis further emphasizes the need for pharmacists to play a key role in optimizing the therapeutic benefit from drug therapy while minimizing the risk of addiction, toxicity, and adverse reactions. Pharmacists have a vital role to play in this setting by optimizing the use of analgesic and adjunct medications and appropriately de-prescribing when harm outweighs benefits. It must be emphasized that the majority of people with chronic painful conditions experience significant pain that impairs their quality of life, resulting in significant physical disability and emotional distress. Chronic pain also affects the patient's significant others such as partners, relatives, employers, co-workers, and friends. An essential part of assessing the appropriateness of pharmacotherapy must include an examination by the clinical pharmacist of BOTH biological and psychosocial factors. Psychosocial factors, such as behavioral presentation, including their emotional state (e.g., anxiety, depression, and anger), perception and understanding of symptoms, and reactions to those symptoms by significant others, provide valuable indicators on a patient's ability to cope with the chronic pain. This multidimensional assessment provides valuable information for assessing the efficacy or the need for ongoing pharmacotherapy or signals the need for a professional psychosocial intervention such as cognitive-behavioral. The clinical pharmacist must be aware of the need for an integrated approach for treating CNCP that must include non-pharmacological as well as pharmacological techniques.

Acute Versus Chronic Pain

Why is chronic pain so difficult to treat? It is difficult because chronic pain is not simply the sustained activation of acute pain pathways and processes. Unchecked pain barrage leads to changes in the central and peripheral processing mechanisms of pain. Sustained acute pain leads to chronic pain conversion, and pain transforms from a physiological adaptive mechanism designed to protect the body from harm to an evolving pathophysiological process. We refer the reader to the excellent review by Woolf [3]. Unchecked pain barrage may also lead to loss of inhibitory pain mechanisms and neurons, which may render analgesics ineffective. These features of acute and

Box 21.1 Acute pain

- Features: Sharp and well-defined onset; short duration
- Etiology: Nociceptive/inflammatory/neuropathic features usually clearly identifiable
- Function: Physiologically adaptive protective function
- Associated with tissue damage: Disappears with tissue healing
- Pharmacotherapy response: Responds well to analgesics and anti-inflammatory agents in usual doses
- Key neuronal fibers: nociception, C; A-δ, pain. A-β touch fiber stimulation decreases pain (gated response)
- Examples: Acute postoperative pain, labor pain, trauma, fractures, soft tissue injury, flail chest, stab injuries

Box 21.2 Chronic pain

- Features: Duration greater than months. No clear onset or onset associated with acute pain cause. Associated with cancer, acute zoster, neurological diseases, hematological disorders
- Etiology: Inflammatory, neuropathic, dysfunctional, nociceptive/neuropathic features become mixed and complex
- Function: Maladaptive, no longer serves a physiological function

- Pharmacotherapy response: Poor or requires higher doses
- Persists months beyond the usual course of acute disease or a reasonable time for an injury to heal usually taken to be 3 months
- Key neuronal fibers, C; A-δ, pain. Stimulation of A-β touch fibers increases pain (loss of gated response)
- Pathological features: *Hyperalgesia,* increased pain from a stimulus that normally provokes pain; there may also be an expanded area of pain. *Allodynia,* pain due to a stimulus that does not normally provoke pain
- Examples: Post-herpetic neuralgia, fibromyalgia, osteoarthritis,

chronic pain can be clinically observed and are identified in Boxes 21.1 and 21.2.

Pain Type

As previously indicated, pain itself is both a sensory and an emotional response. There is enormous heterogeneity encompassed with the terms pain and chronic pain. For the purposes of this chapter, chronic pain will be taken as chronic non-cancer pain (CNCP), as there are differences in the etiology and in the risk-benefit of pharmacotherapy compared to cancer pain. The pharmacist monitoring analgesia must look for the general features of nociceptive and neuropathic pain. The International Association for the Study of Pain (IASP) defines *nociceptive pain* as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors" [4]. Nociceptive pain denotes a normal functioning of the somatosensory nervous system in direct contrast to neuropathic pain. The IASP defines *neuropathic pain* as "pain caused by a lesion or disease of the somatosensory nervous system" and is further divided into central and peripheral neuropathic pain [5].

The IASP has recently added the term *nociplastic pain*, which arises from altered nociception despite no clear evidence of actual or threatened tissue damage, causing the activation of peripheral nociceptors or evidence of a disease or lesion of the somatosensory system causing the pain. By this very definition, nociplastic pain denotes a pathological condition for which drug responsiveness will vary. Critically, pharmacotherapy responsiveness is significantly different for nociceptive vs. neuropathic pain. Neuropathic pain responds poorly to standard opioid therapy, but it may respond to higher opioid doses or opioids with unique effects on other receptors such as methadone. Because CNCP patients will usually present with a complex mixture of nociceptive, nociplastic, and neuropathic pain, pharmacotherapy will be multimodal in approach. The need for non-pharmacological interventions such as cognitive-behavior therapy cannot be over-emphasized due to the sensory-emotional effect of pain.

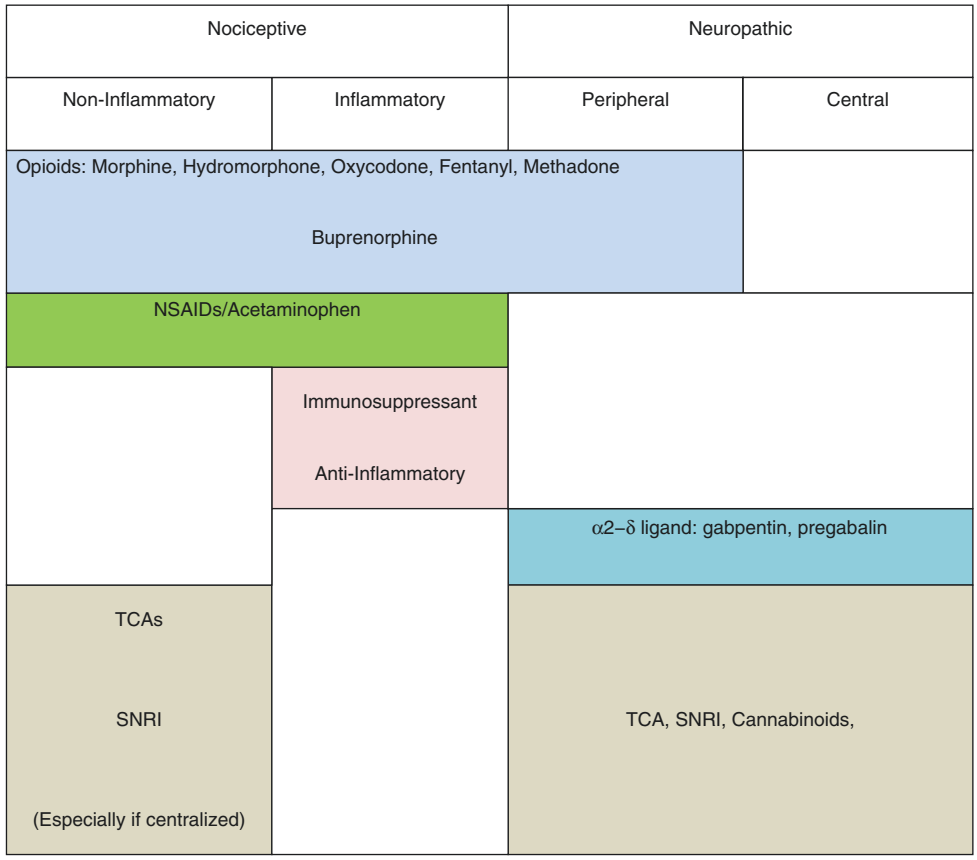
General pharmacotherapy approaches to pain mechanisms are summarized in Tables 21.1 and 21.2.

Risk Factors

An extensive list of risk factors has been identified, especially in the postsurgical literature looking at the risk of acute to chronic conversion. The most common pooled risk factors include the following [8, 9]:

- Psychological vulnerability (catastrophizing)
- Anxiety or depression
- Female gender
- Younger age (adults)
- Genetic predisposition
- Inefficient diffuse noxious inhibitory control (DNIC)
- Descending pathway of pain inhibition
- Nerve damage due to injury or surgery
- History of poor acute pain management
- History of poor response to common analgesics

Table 21.1 Pharmacotherapeutic recommendations by pain type [6, 7]



SNRI serotonin norepinephrine reuptake inhibitors, *TCAs* tricyclic antidepressants

Table 21.2 Drug class recommendations for chronic non-cancer pain

Drug class	Pain type and dosing recommendations
Acetaminophen	Mild to moderate nociceptive pain; optimize prior to adding other analgesics; monitor for hepatic damage
Oral NSAID: Ibuprofen, naproxen, diclofenac	Inflammatory pain, musculoskeletal pain. Use the lowest effective dose for the shortest time period Useful with inflammatory pain states. Note that the risk of GI and cardiovascular complications increases with increasing age
Topical NSAID: Diclofenac	Inflammatory, musculoskeletal pain. Decreased systemic exposure to the drug, with a decrease in GI and cardiovascular toxicity
Opioids	Nociceptive pain: lowest effective dose, shortest duration. Adequate trial must include an assessment of quality of life and coping. Possible role for methadone and buprenorphine in neuropathic pain
Tricyclic antidepressants (TCA): Amitriptyline, nortriptyline	Neuropathic pain: central and peripheral. TCAs are very effective if patients can tolerate significant anticholinergic effects. Caution in frail elderly: Assess anticholinergic burden
SNRI: Duloxetine	Neuropathic pain. May also be useful for osteoporotic pain due to changes in centralized pain processing.
Alpha-D2 calcium blockers: Gabapentin, Pregabalin	Neuropathic pain: peripheral and central. Use lowest effective dose
Cannabinoids/standardized medical marijuana products	Neuropathic pain: Peripheral and central

NSAID nonsteroidal anti-inflammatory agent, *SNRI* serotonin norepinephrine reuptake inhibitors

Goals of Therapy

Where possible, the goals of therapy should always attempt to treat the underlying cause of the pain, reduce pain, improve quality of life, and improve functioning. Pharmacists need to be aware that pain reduction alone is an insufficient goal. Improved quality of life needs to be a major focus for treating chronic pain because analgesics will likely only achieve modest pain reductions. Pharmacists need to work closely with patients to determine the patient's ultimate pain goals. Oftentimes, the patient may not be seeking direct pain relief but relief from the unremitting effects pain has on other physiological functions such as sleep and mood. Restoring previous function is often not possible, but it may be possible to improve physical, emotional, and social functioning to yield an improved quality of life through an improved ability to perform the activities to which the patient ascribes significant meaning. Pharmacists need to work with the patient to minimize inappropriate medication use while advocating for appropriate medication use.

Role of the Pharmacist in Management

A meta-analysis by Hadi et al. in 2014 concluded that pharmacist-led medication review reduces pain intensity and improves physical functioning and patient satisfaction [10]. Additionally, they concluded that there was weak evidence that a pharmacist medication review may also prevent or stop adverse events from occurring. Given the current opioid crisis and the ongoing clinical problem of poorly treated chronic pain, the pharmacist has a significant role to play. Medication review or reconciliation with the patient's pain goals and psychosocial functioning is a vital role for the pharmacist. Critically, the clinical pharmacist needs to be aware that chronic pain affects more than just the individual patient. Chronic pain has a pervasive and invasive effect on the patient's significant others, including spouses, partners, relatives, employers, coworkers, and friends. Thus, treatment must include not only a comprehensive assessment of the pathophysiology and biology of the pain but also an assessment or at least an awareness of psychosocial and behavioral effects. Due to the multi-faceted nature of pain as an emotional and sensory event, anxiety, depression, and anger are part of the assessment and treatment. Turk and Meichenbaum suggest that for chronic pain assessments, it is important to ascertain the following key factors [11, 12]:

1. What is the extent of the patient's physical impairment?
2. To what extent is the patient suffering, disabled, or unable to enjoy the usual activities?
3. Is there any evidence of symptom amplification?

These factors should be considered during the pharmacist's pain and medication review. Escalation in these domains despite an appropriate trial of pharmacotherapy could be used to alert the medical team that pharmacotherapy is no longer providing adequate benefit and emphasize the need for non-pharmacological interventions by other health professionals.

Pharmacotherapy is only a part of the therapy that is used to treat CNCP. The perception and meaning of pain is a complex interaction of neuronal mechanisms and the emotional response to those stimuli. CNCP cannot be treated with drugs alone. Pharmacists need to be aware of non-pharmacological modalities, especially when a medication review reveals inadequate analgesia and the patient demonstrates signs and symptoms of increasingly maladaptive coping. Cognitive and behavioral techniques, which may include distraction, goal setting, and exercises, have been demonstrated to be both safe and effective [13]. Exercise programs, tai chi, and yoga have also been shown to help reverse deconditioning and improve mood and the sense of well-being. A multidisciplinary team including psychologists, social workers, physiotherapists, and occupational therapists is essential for teaching appropriate exercises and coping strategies and providing emotional support [13, 14]. In fact, most CNCP patients ultimately develop a strategy of coping

that involves all these techniques and disciplines. Our goal as clinical pharmacists is to optimize the beneficial use of drug therapy in this process while emphasizing de-prescribing for maladaptive drug use to help the patient find the best balance of pharmacological and non-pharmacological techniques to improve quality of life.

Initial Pain Assessment

An initial pain assessment should seek to comprehensively understand the patient's pain syndromes with an integrated review of the pharmacological and non-pharmacological interventions that have been both successful and failed. An algorithm for assessment is summarized in Box 21.3. As part of the patient's best-possible medication history (BPMH), pharmacists should assess the response the patient received from each medication. CNCP patients will often have good memory recall of drug therapy that failed and drug side effects that were particularly troublesome. Statements such as "would never try that drug again" or "that drug was useless" may indicate these issues. Pharmacists should look for patterns of responsiveness or refractoriness in order to help assess pain type or detect patterns of abuse. As marijuana and marijuana products are scheduled for legalization in Canada, medical marijuana prescriptions will no longer be required. Pharmacists need to add a discussion on marijuana use into their routine pain assessment. This assessment must be completely nonjudgmental, focusing first on whether marijuana has been used in the past or the patient is currently using marijuana. The next step is to determine if the marijuana product has been effective in reducing pain or symptoms related to pain such as anxiety and mood. The pharmacist should then probe for evidence of harm such as sedation, dizziness, or a deterioration in mood and increased isolation. Currently, evidence exists for the use of cannabinoids in neuropathic pain; however, a popular view exists espousing the use of marijuana as a panacea for all chronic pain conditions [7]. Patients need to be advised on the current level of evidence and helped to evaluate their own marijuana consumption for efficacy and toxicity. Cannabinoid hyperemesis syndrome has been observed with increasing frequency. Patients present with increasing nausea and emesis that is relieved by taking hot showers. The syndrome resolves with supportive care and the cessation of marijuana products [15].

Box 21.3 Pharmacist assessment algorithm for a pharmacotherapy review

1. Physical assessment: SCHOLAR, symptoms, characteristics, history, onset, location, aggravating, and remitting factors. SOCRATES, site, onset, character, radiation, associations, time course, exacerbating and relieving factors, severity
   (a) Pain intensity: numerical scale 0 no pain and 10 worst pain (do not focus solely on intensity)
   (b) Pain type: to determine the appropriateness of pharmacotherapy
      (i) Descriptors of neuropathic pain: sharp, shooting, stabbing, burning, electric shocks
      (ii) Descriptors of nociceptive pain: aching throbbing, steady, dull (if visceral: aching, gnawing, cramping, squeezing)
   (c) Pain duration: When did it start? How long? Has it changed over time?
2. Patient's pain goal
   (a) Includes pain score
   (b) Goals such as "sleeping through the night"
   (c) Increased ability to perform activities of daily living (ADLs)
3. Pharmacotherapy review
   (a) Appropriate for pain type: nociceptive and neuropathic features
   (b) Appropriate for pain intensity
   (c) Opioid appropriateness review: Includes risk for addiction and abuse

(d) Cannabinoid review: neuropathic pain vs. personal trials of cannabidiol (CBD), tetrahydrocannabinol (THC)

4. Signs of psychosocial stress
   (a) ACT-UP (see text)
   (b) Pharmacotherapy for anxiety and depression
   (c) Non-pharmacological interventions: include counseling, cognitive behavioral therapy (CBT), etc.

Ongoing Assessment of a Patient Diagnosed with Chronic Non-cancer Pain

Chronic non-cancer pain should never be viewed as static, nor should chronic pain be viewed as simply sustained activation of acute pain pathways. Chronic non-cancer pain represents a heterogeneous pathophysiological process of its own. Due to changes in central and peripheral pain processing, acute pain pharmacotherapy is often ineffective, especially in usual drug doses. Patients must be re-assessed in order to determine changes in pain processing. In addition, the occurrence of new diseases and complex changes may render previous treatments similarly ineffective. Clinical pharmacists must be able to provide sufficient assessment so that the efficacy and toxicity of pharmacotherapy can be correctly monitored and patients properly advised to seek additional treatment and/or support from their pain specialist, primary care provider, or psychologist. Pharmacists need to be aware that pharmacotherapy alone will be insufficient for the optimal treatment of chronic non-cancer pain. An interdisciplinary approach that includes all possible treatment modalities, including nerve blocks, surgical interventions, cognitive behavioral therapy, occupational therapy, physician therapy, and even spiritual support, must be considered using shared decision-making with the patient.

Assessment Tools and Scales

A. *Pain Overall Assessment*
   1. *SCHOLAR*: *S*ymptoms, *C*haracteristics, *H*istory, *O*nset, *L*ocation, *A*ggravating, and *R*emitting Factors.
   2. *The SOCRATES* acronym lends itself well to pain assessments: *S*ite, *O*nset, *C*haracter, *R*adiation, *A*ssociations, *T*ime Course, *E*xacerbating and Relieving Factors, *S*everity.

   Comments on Use: It is best to use a consistent approach for assessment from one visit to the next to allow for serial assessments to be compared with less bias.

B. *Pain Intensity Assessment: Numerical Scale*

   0: No Pain 10: Worst Pain
   Comments on Use: Pain intensity should always be combined with assessments of the quality of life and coping with the pain.

C. *Opioid Abuse Risk: Screener and Opioid Assessment for Patients with Pain (SOAPP)® Version 1.0-SF* [16]

   Please answer the questions below using the following scale:
   0 = Never, 1 = Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often
   1. How often do you have mood swings?
   2. How often do you smoke a cigarette within an hour after you wake up?
   3. How often have you taken medication other than the way that it was prescribed?
   4. How often have you used illegal drugs (for example, marijuana, cocaine, etc.) in the past 5 years?

5. How often, in your lifetime, have you had legal problems or been arrested?

Comments on Use: Assess all items answered with ε 3. It is best to avoid opioid trials in patients with high risk but with appropriate clinical oversight even with high risk may be managed on opioids. This requires significant patient-team cooperation and should only be attempted with an experienced pain physician.

D. *Psychosocial Screening: ACT-UP* [17]

1. Activities: How is your pain affecting your life (i.e., sleep, appetite, physical activities, and relationships)?
2. Coping: How do you deal/cope with your pain (what makes it better/worse)?
3. Think: Do you think your pain will ever get better?
4. Upset: Have you been feeling worried (anxious)/depressed (down, blue)?
5. People: How do people respond when you have pain?

Comments on Use: Increasing coping difficulties are a sign that the current treatment is inadequate. Drug therapy may require modification, but this should be combined with referral or recommendation for psychosocial treatment modalities from other healthcare professionals. Pharmacists are in a good position to advocate for these modalities.

E. *Neuropathic Pain Symptom Inventory (NPSI)*

The NPSI is summarized in Table 21.3. The NPSI should be performed only after a discussion on pain quality that identifies pain descriptors indicative of an increase in or the appearance of pain that is potentially neuropathic. The NPSI can then be performed and the results shared with the patient and the patient's pain physician for a more extensive and precise assessment in accordance with neuropathic pain diagnostic guidelines.

Table 21.3 Neuropathic Pain Symptom Inventory (NPSI) [18]

Severity of spontaneous pain		
Q1. Does your pain feel like burning	0 no burning, 10 worst burning imaginable	
Q2. Does your pain feel like squeezing?	0 no squeezing, 10 worst imaginable squeezing	
Q3. Does your pain feel like pressure?	0 no pressure, 10 worst imaginable pressure	
Q4. During the past 24 h, has your spontaneous pain been present?	Permanently 8–12 hour 4–7 hour 1–3 hour <1 hour	( ) ( ) ( ) ( ) ( )
Severity of painful attacks		
Q5. Does your pain feel like electric shocks?	0 no electric shocks, 10 worst imaginable electric shocks	
Q6. Does your pain feel like stabbing?	0 no stabbing, 10 worst imaginable stabbing	
Q7. In the past 24 h, how many of these pain attacks have you had?	>20 11–20 6–10 1–5 None	( ) ( ) ( ) ( ) ( )
Severity of provoked pains		
Q8. Is your pain provoked or increased by brushing the painful area?	0 no pain, 10 worst imaginable pain	
Q9. Is your pain provoked or increased by pressure on the painful area?	0 no pain, 10 worst imaginable pain	
Q10. Is your pain provoked or increased by contact with something cold on the painful area?	0 no pain, 10 worst imaginable pain	
Severity of abnormal sensations		
Q11. Do you feel pins and needles?	0 no pins and needles, 10 worst imaginable pins and needles	

Table 21.3 (continued)

Q12. Do you feel tingling?	0 no pins and needles, 10 worst imaginable pins and needles
Total intensity scores	Subscores
1. Q1 =	Burning (superficial) spontaneous pain: Q1 = /10
2. (Q2 + Q3) =	Pressing (deep) spontaneous pain (Q2 + Q3)/2 = /10
3. (Q5 + Q6) =	Paroxysmal pain: (Q5 + Q6)/2 = /10
4. (Q8 + Q9 + Q10) =	Evoked pain: (Q8 + Q9 + Q10)/3 = /10
5. (Q11 + Q12) =	Paresthesia/dysesthesia: (Q11 + Q12)/2 = /10
(1 + 2 + 3 + 4 + 5) = /100	

Note: Q4 and Q7 are for assessing the persistence of the pain but do not get scored

Opioid Appropriateness

Opioid prescribing rates in Canada are among the highest in the world [19]. Substantial risks such as addiction and overdose accompany opioid therapy, and these risks have significant individual and societal impact. In light of the opioid crisis, the Canadian Guideline for Opioid Use in Chronic Non-cancer Pain recommends the optimization of non-opioid strategies before considering opioid therapy [19]. Despite best efforts to optimize non-opioid pharmacotherapy and behavioral strategies, a proportion of patients will suffer from persistent problematic pain. It is important to acknowledge that there will be a subset of patients that will derive a functional benefit from opioid therapy and a subset that will suffer a serious adverse outcome such as addiction and a fatal or nonfatal overdose. When assessing a patient with persistent problematic pain, clinicians are challenged with balancing the potential benefit, including functional improvement and reduction in pain scores, with the serious adverse outcomes of opioid therapy.

Recent literature has identified patient factors that are associated with an increased risk of addiction and a fatal or nonfatal overdose including current or past substance abuse disorder and an active psychiatric disorder [19]. The Opioid Risk Tool (ORT) has been used to screen for the risk of opioid misuse; however, its predictive value has not been validated. When considering a trial of opioid therapy, the medical history should include questions to screen for a current or past history of substance abuse and psychiatric disorders. Opioids are not recommended for patients with current or past substance abuse disorders [19]. For patients with an active psychiatric disorder, it is recommended that the condition be stabilized before a trial of opioids is initiated because of the impact on pain perception and expression [19].

Table 21.4 Opioid trial initial patient assessment

Indication	Effectiveness
Characteristics of pain Nociceptive vs. neuropathic (neuropathic is opioid resistant) Persistent vs. intermittent (continuous dosing for persistent pain) Opioid use in previous 6 months Non-pharmacological strategies	MED <50 mg if opioid naïve or <90 mg if on long-term opioid therapy Note: Some patients may benefit from higher doses; suggest a second opinion If the dose exceeds accepted guidelines Consider taper, rotation or referral

MED morphine equivalent doses

When an opioid trial is initiated, there are a number of considerations for determining appropriateness (Table 21.4) [20, 21]. Therapy should be prescribed at the lowest dose and for the shortest duration, usually no more than 4 weeks. Although the evidence is not strong, Naloxone

Table 21.5 Clinical features of opioid misuse

1. Altering the route of delivery
2. Accessing opioids from other sources
3. Unsanctioned use
4. Drug seeking
5. Repeated withdrawal symptoms
6. Accompanying conditions (addiction to another drug)
7. Deteriorating social function
8. Views on opioid medication

kits should be considered for all patients, especially those who are identified as at risk of toxicity due to high dose, medical history, or comorbidities. Naloxone is an opioid antagonist that can temporarily reverse an opioid overdose. These kits typically include three doses of naloxone and the supplies to administer the injection. During an opioid trial, additional assessment is warranted to identify progress toward functional goals, emerging risk factors for adverse outcomes, and signs of opioid misuse disorder. Communication and collaboration with the patient and other healthcare providers are critical. The patient interview should include a patient-centered functional assessment. Patients should be screened for the clinical features of opioid misuse (Table 21.5) [21]. Tools such as the Screener and Opioid Assessment for Patients with Pain (SOAPP)® can be useful in recognizing aberrant drug-related behaviors [19]. The morphine equivalent doses (MED) should be calculated at each follow-up as the risk of unintentional overdose and death increases as the prescribed dose of opioids increases, with the most significant change in rates at >50 mg, if opioid naïve, and >90 mg MED, if on long-term opioid therapy [20].

Follow-up Assessments

Adherence

Patient adherence in CNCP is almost always linked to the toxicity or efficacy of the drug therapy. Problematic or ineffective therapies are quickly identified by the patient and discarded. Patients may become quite manipulative to access the therapies that have historically worked the best with the least amount of side effects. When assessing drug adherence, pharmacists should evaluate dispensing time intervals, dispensing events at other pharmacies, double doctoring, and use of other medications that may alter the current drug therapy. This becomes especially important for the monitoring of both the safety and efficacy of long-term opioid therapy.

Control

The clinical pharmacist needs to be alert for changes in the patient's pain syndrome. Due to the chronicity of the disease, patients and clinicians may conclude the disease is static with little need for close monitoring or therapy adjustment. CNCP should be viewed as a dynamic ongoing disease state that will demonstrate acute exacerbations in response to concomitant disease or infections and may require aggressive management. A CNCP patient with acute exacerbation in pain intensity must be immediately worked up to determine if the pain represents an aggravation of the existing condition or the development of a new one. New pain symptoms require a thorough and complete new pain assessment with the intent to look for new underlying conditions. This includes appropriate laboratory and imaging studies. Patients with chronic pain may be at risk for a delay or underdiagnosis of new diseases states such as CNCP that may mask the development of cancer.

Adverse Drug Reactions

The most common reasons for poor drug adherence are inadequate response (ineffective treatment) and adverse drug reactions. Common adverse reactions vary in severity and may be managed with careful dose titration. However, severe adverse drug reactions may warrant the discontinuation of the drug entirely. Table 21.6 provides a list of common adverse reactions and

Table 21.6 List of most common and important drug complications in patients with CNCP[a]

Drug	Common adverse reactions/ precautions	Red flag complications
Opioids (morphine, hydromorphone, fentanyl, methadone, buprenorphine) Codeine (NOT recommended)	Sedation, dizziness, nausea, vomiting, constipation, sweating	Addiction/diversion Hallucinations Neurotoxicity: hallucinations, hyperalgesia, myoclonus, seizures Hypogonadism QTc prolongation: Avoid in long QT syndrome Overdose: respiratory depression Drug diversion
Acetaminophen	Usually no adverse reactions but may cause nausea, vomiting, loss of appetite	Hepatic failure: overdose or chronic dose
NSAIDs	GI: vomiting, bloating, diarrhea, constipation, mucosal erosions Renal: ↓GFR, Na and water retention, edema, CVS thrombotic events, increased blood pressure, congestive heart failure, palpitations CNS: headache, fatigue, insomnia, vertigo, seizures Other: Asthma attacks, urticaria, neutropenia	GI bleeding Renal failure Thrombotic events CHF
α2-δ Ca2+ Blockers Gabapentin Pregabalin	Dizziness, drowsiness, weakness, tired feeling; Nausea, diarrhea, constipation; Blurred vision; Headache; Breast swelling; Dry mouth; or. Loss of balance or coordination.	Ataxia with increased fall risk especially in the frail elderly Delirium
SNRI Venlafaxine Duloxetine	Dizziness, Nausea, Dry mouth, Sweating, Tiredness, Insomnia, Anxiety or agitation, Constipation	Serotonergic syndrome: Diarrhea may be an early symptom Symptoms include high body temperature, agitation, increased reflexes, tremor, sweating, and dilated pupils
SNRI/Opioid Tramadol (NOT recommended)		Serotonergic syndrome CYP2D6 ultrametabolizers: CNS sedation, respiratory depression, death
Tricyclic antidepressants Amitriptyline Nortriptyline	Anticholinergic side effects Dry mouth, constipation	Delirium Cognitive impairment
Cannabinoids Nabiximols (Sativex®)	Sedation Dizziness	Cannabinoid hyperemesis syndrome: Paradoxical increase in nausea and emesis often relieved by hot showers. Stop cannabinoid therapy

NSAID nonsteroidal anti-inflammatory agent
[a]Adapted from Refs. [6, 7, 22–33]

precautions combined with "red flag" complications that necessitate the discontinuation of that drug therapy.

Complications

CNCP often presents as a result of other disease states, but CNCP may also result in significant complications. Complications of CNCP may be related to de-conditioning, hormal effects of chronic pain and stress and neuropsychiatric complications. CNCP results in a significant loss in activity leading to an underappreciated increase in deconditioning. This results in an increased loss of mobility and obesity and may exacerbate the development of concomitant diseases such as type 2 diabetes mellitus. Disruption of normal biomechanics can lead to muscle underuse and atrophy with compensatory muscle overuse with tissue degeneration and damage. The situation is exacerbated by obesity, and the patient needs to be encouraged to undertake some form of exercise to prevent atrophy and damage combined with efforts to attain a healthy weight.

CNCP is also associated with excess catecholamine production, especially adrenalin release combined with cortisol release. Since acute pain is designed for a protective purpose, chronic pain can result in an overactivation of the sympathetic nervous system and a perpetual state of arousal. This may feed directly into feelings of fear, anxiety, or dread. It may also contribute to the maintenance of the pain state.

Neuropsychiatric symptoms, especially in patients with unremitting symptom control and increased difficulty in coping can result in insomnia, memory loss, cognitive decline, depression, and suicidal ideation. Escalating opioid doses with increasing generalized pain may indicate opioid-induced hyperalgesia and attempts to use opioids as anxiolytics and should be carefully evaluated [22]. The risk of an accidental or intentional opioid overdose increases with an increasing morphine equivalent daily dose. Pharmacists should pay critical attention to increasing depression and anxiety and be alert for comments related to a sense of hopelessness or futility and suicidal or end-of-life comments. In Canada, legislation that allows for medical assistance in dying (MAID) has brought the discussion of euthanasia more into the open. CNCP patients may ask their pharmacist about the drugs used for MAID, and the reason for this interest should be carefully explored with the patient.

Clinical Pearls

- Assess the efficacy of pharmacotherapy, including pain intensity, pain quality, AND psychosocial indicators of coping.
- Assess drug adherence by evaluating dispensing time intervals, dispensing events at other pharmacies, double doctoring, and the use of other medications that may affect opioid therapy.
- Opioid-naive patient: Assess efficacy based on pain intensity score, and assess the effect on psychosocial aspects using ACT-UP. Look for improvement in quality of life as indicated by the ability to perform ADLs and meaningful activities. A decreased ability to participate in meaningful activities should be discussed with the patient and physician. Initial opioid dose is recommended to be <50 oral morphine equivalents (OME) per day. Duration of therapy should not exceed 1 week without reassessment. If doses are increased, they should be titrated upward, and the individual should be monitored for pain control and/or function improvement.
- For individuals using long-term opioid therapy, total doses should not typically exceed 90 OME/day and the individual should not receive more than a 30-day supply. Assess as indicated for the opioid-naive patient. Monitor for hyperalgesia, increased pain that may be generalized and not typical of usual chronic pain. Opioid neurotoxicity can induce hyperalgesia. Monitor for sedation, visual disturbances, hallucinations, and myoclonus, which could indicate opioid neurotoxicity.
- Assess patient use of marijuana products. What product are they taking? What is the THC, CBD content? Has the drug been effec-

tive in relieving pain? Relieving anxiety? What are the side effects? Dizziness? Sedation? Has the marijuana product allowed for a reduction in other prescription drug use? Monitor for ataxia, increased sedation, and confusion or delirium. Monitor for increased nausea with emesis relieved by hot showers which could indicate cannabinoid hyperemesis syndrome.

- Assess the patient for the need for non-pharmacological interventions such as cognitive-behavioral techniques.

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Part IV

Specialized Assessments

Pharmacokinetic Assessment

22

Sherif Hanafy Mahmoud

Chapter Objectives

1. Discuss the clinical relevance of pharmacokinetic concepts
2. Apply the basic pharmacokinetic principles in therapy assessments
3. Identify the concepts and rationale for therapeutic drug monitoring (TDM)
4. Apply pharmacokinetic principles in TDM

Background

Pharmacokinetics is the study of what happens to the drug in the body following its administration. It is the study of the drug journey from the time of its administration to its elimination. It involves four distinct processes: absorption, distribution, metabolism and excretion (ADME). Understanding basic pharmacokinetic principles is essential in day-to-day clinical pharmacy practice (Table 22.1). It allows answering many clinical questions such as:

- What is the intravenous dose of morphine, if my patient is currently on 10 mg oral morphine?
- My patient got started on vancomycin, when do I need to measure a level?
- My patient experienced a serious adverse reaction from rivaroxaban, when it is going to be out from his system?
- Do I need to load this drug? If yes, what is the loading dose?

Table 22.1 Applications of pharmacokinetics in therapy assessments

Pharmacokinetic applications	Pharmacokinetic (PK) parameter(s) utilized
Therapeutic drug monitoring	All PK parameters
Prediction of the extracorporeal drug removal by renal replacement therapies such as hemodialysis	Protein binding, volume of distribution, clearance
Estimation of IV to PO dose conversion	Bioavailability, salt factor
Estimation of the drug loading dose	Volume of distribution, target steady state concentration, bioavailability
Determination of the time it takes for the drug to reach steady state	Half-life
Determination of how long it takes for the drug to be out from the system	Half-life
Assessment of pharmacokinetic drug interactions	All PK parameters
Assessment of missed drug doses	Half-life, pharmacokinetic-pharmacodynamic relationship

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- Carbamazepine plasma concentration came back as 20 μmol/L, what should I do?
- I forgot to take the morning dose of my medicine, what should I do?

This chapter will go over the basic pharmacokinetic principles by discussing the ADME system and its applications in patient's therapy assessment. Then, the rationale and approach to therapeutic drug monitoring will be discussed.

Basic Pharmacokinetic Concepts Related to ADME System

Absorption

Bioavailability

Following administration by any route, with the exception of the intravenous (IV) route, drugs need to be absorbed to reach the systemic circulation. The fraction of the administered drug that is absorbed is called bioavailability or "F," and it reflects the extent of drug absorption. This depends on the physicochemical characteristics of the drug and the characteristics of the absorption site such as blood supply and pH. The bioavailability for the intravenous route is 100% because the drug is directly delivered to the bloodstream. On the other hand, other routes such as oral, intramuscular, and subcutaneous routes generally have bioavailability values of less than 100%. Knowledge of the bioavailability is very helpful in day-to-day clinical practice. Bioavailability assists in getting an idea of the systemic exposure of the drug (how much drug is absorbed into the bloodstream) and, hence, the equivalent dosages when switching among different routes. To illustrate, Table 22.2 depicts the oral bioavailability values of select drugs. For drugs with almost complete oral bioavailability such as phenytoin and valproic acid as shown in the table, the iv to oral dose conversion ratio is one to one. For example, 500 mg/day of IV valproic acid is equivalent to 500 mg/day of the oral formulation. On the other hand, other drugs such as morphine and propranolol have significantly lower oral bioavailability secondary to the extensive first pass metabolism. While assessing patients' medications, pharmacists should expect lower intravenous dosages when compared to oral regimens for drugs with low oral bioavailability. For example, 30 mg oral morphine has been suggested to be equivalent to 10–15 mg of parenteral morphine. Furthermore, drugs that have no oral bioavailability (i.e., not absorbed) are not expected to be used orally to treat systemic illnesses. For example, vancomycin is not absorbed orally and should be given intravenously when used to treat systemic infections.

Table 22.2 Oral bioavailability of select drugs

Drug name	Bioavailability
Phenytoin	90–100%
Valproic acid	90–100%
Vancomycin	0%
Morphine	17–33%
Propranolol	25%

Salt Factor

The second concept related to absorption is the salt factor, or "S." Some drugs are available in different salt forms and/or pro-drugs. The salt factor is the fraction of the pro-drug or salt form that contains the pharmacologically active drug. With regards to clinical relevance, the salt factor is important in determining the equivalent dosages of different salt forms of the drug. For example, while the parenteral and oral extended release formulations of phenytoin contain phenytoin sodium salt, immediate release tablets and suspension contain the free phenytoin acid form. Phenytoin sodium contains 92% of the free phenytoin acid form. In other words, it has a salt factor of 0.92. However, this difference is not clinically significant in most patients owing to the long half-life of phenytoin. On the other hand, the salt factor for other drugs is clinically significant, and it should be included in equivalent dosage calculations. For example, aminophylline, the ethylene diamine salt of theophylline, contains 80% theophylline (salt factor = 0.8). In other words, when switching aminophylline to theophylline, aminophylline dose needs to be multiplied by 0.8.

Rate of Absorption

The third concept is the rate of absorption of the drug. This is best illustrated when sustained release (SR) formulations of the drug are compared with immediate release ones. As shown in Fig. 22.1, immediate release formulations release the drug rapidly with the potential for higher maximum concentrations (C_{max}) than the SR formulation; however, their effect goes away quicker than the SR formulations. The rate of drug absorption determines the onset of effect and time to peak concentration and is beneficial in formulation conversions. For example, the extended release formulations of diltiazem slowly release the drug in the gastrointestinal tract resulting in prolonged duration of action and hence are administered once daily. On the other hand, diltiazem immediate release formulation quickly releases the drug but owing to the drug's short half-life, it needs to be dosed four times daily. If a patient on diltiazem SR 240 mg oral once daily was unable to swallow, switching to the liquid formulation could be a reasonable alternative. However, the 240 mg dose will need to be given in four divided doses; otherwise, giving the full liquid dose at once will put the patient at risk of bradycardia and hypotension. Pharmacists play an important role in drug formulation conversions. While assessing patients' medication regimens, it is essential to assess if patients are administering their controlled release medications appropriately.

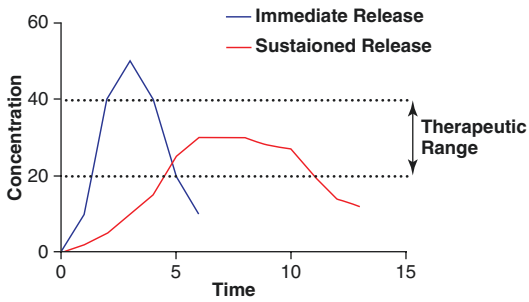


Fig. 22.1 Concentration vs. time profile of immediate and sustained release formulations

Pharmacokinetic Drug Interaction: Absorption

Pharmacokinetic drug interactions can occur at any stage during the journey of the drug in the body. Drug-drug and food-drug interactions might lead to alterations in the rate and extent of drug absorption. For example, co-administration of levothyroxine and iron supplements leads to reduced bioavailability of levothyroxine and hence reduction in its efficacy [1]. Administering levothyroxine and iron supplements should be spaced with at least 4 h to avoid that interaction. Another example is phenytoin. Administering phenytoin along with feeds in tube-fed patients could drastically reduce phenytoin bioavailability by up to 80%, putting the patient at risk for breakthrough seizures. Holding feeds 2 h before and 2 h after phenytoin administration is recommended. Pharmacists need to be vigilant in identifying the potential for these interactions. Iron, calcium, aluminum and magnesium salts, polystyrene, and cholestyramine are examples of agents commonly implicated in absorption interactions. It is important to check drug interaction reference and administration with food guides while assessing patients' medication regimens.

Distribution

Volume of Distribution

Once the drug is absorbed or given intravenously, it distributes via systemic circulation to different tissues in the body. The extent of drug distribution depends on many factors such as the drug's lipophilicity, tissue affinity and protein binding. Volume of distribution (V_d) is the apparent volume in which the drug distributes. It reflects the extent of drug distribution in the body. Drugs with high volume of distribution are more distributed in the body compartments than drugs with low volume distribution. With regard to clinical relevance, volume of distribution is helpful in determining the loading dose. Administering loading doses of drugs could be of value to rapidly attain therapeutic concentrations. The intravenous loading dose can be calculated by multiplying the drug's desired steady state

Table 22.3 Protein binding and volume of distribution of select drugs

Drug	Volume of distribution	Percent protein binding
Phenytoin	0.7 L/kg	90%
Vancomycin	0.7 L/kg	55%
Levetiracetam	0.5–0.7 L/kg	<10%
Amiodarone	66 L/kg	>96%

concentration (C_{ss}) by its volume of distribution (Eq. 22.1). If the same amount of the drug is added to two containers with different volumes, different concentrations will result. Therefore, drugs with high V_d require higher doses than drugs with low V_d to obtain the same concentration. To illustrate, as seen in Table 22.3, amiodarone has a volume distribution of 66 liters per kilogram, suggesting extensive distribution in the body compartments. As a result, amiodarone needs to be loaded with a much higher dose compared to drugs with low volume of distribution in order to rapidly target concentrations.

$$\text{Loading dose} = \text{desired}\, C_{ss} \times V_d \quad (22.1)$$

It is important to note that patient-specific factors that might alter V_d should be taken into consideration when pharmacists are assessing the appropriateness or calculating a drug loading dose. These factors include obesity, conditions of altered protein binding (see next section), patient's weight and conditions associated with altered body volume status such as pregnancy, cystic fibrosis and burns. Drug-specific information pertaining to Vd values in various disease states could be found in the PK section of drug monographs and PK studies [2].

Protein Binding

Another important concept that has a major influence on the pharmacokinetics of drugs is protein binding. Drugs can bind to plasma albumin, alpha acid glycoprotein, or lipoproteins. Generally, basic drugs bind to alpha acid glycoprotein while acidic ones bind to albumin. The higher the extent of protein binding is, the smaller the volume of distribution of the drug. Most drugs exist in two forms: free and bound. The bound fraction of the drug is restricted to plasma while the free fraction is available for distribution to tissues. Generally, the free fraction is the pharmacologically active form and is the one that is available for elimination. Therefore, any factor that can alter protein binding has the potential to affect the drug's efficacy, clearance, and volume distribution. Table 22.4 depicts a summary of the factors that might affect protein binding of drugs that pharmacists need to be aware of.

Table 22.4 Factors affecting protein binding of drugs

Altered plasma protein concentration	Conditions associated with low albumin concentration: Hepatic failure Nephrotic syndrome Burns Malnutrition Aging Critical illness This results in increase in the free fraction of acidic drugs. Conditions associated with increase in alpha acid glycoprotein: Inflammatory condition such as rheumatoid arthritis. This results in decrease in the free fraction of basic drugs.
Displacement from plasma protein binding	Diseases associated with protein binding displacement Renal failure (uremic substances) Hyperbilirubinemia Drug-drug interactions

Drug Levels

Drugs where therapeutic drug monitoring is of value usually have their recommended reference range reported. The reference range is the range of drug concentrations below which the drug is most probably ineffective and above which the drug is most probably toxic. It is important to mention that reference ranges are based on retrospective studies and population normals and are not carved in stone. Drugs can be effective at concentrations below the recommended range or toxic at concentrations within the range. Therefore, reference ranges can be used as a tool to assess patient's drug therapy rather than an ultimate goal to target (treat the patient, not the level). Measuring routine levels is not recommended. Drug levels are only measured if

they are indicated (discussed later in the chapter) and are generally measured at steady state. However, pre-steady state levels can be beneficial in some situations to determine the adequacy of the dosage.

Pharmacokinetic Drug Interaction: Distribution

Generally, highly protein bound drugs (protein binding ≥ 90%) are prone to drug interactions secondary to protein binding displacement. As seen in Table 22.3, phenytoin and amiodarone are extensively protein bound and are subject to protein binding displacement. On the other hand, levetiracetam and vancomycin are not highly protein bound, making them not prone to interactions via protein binding displacement. Drug-induced alteration in protein binding might be clinically significant with initiation of therapies or dose changes. With chronic administration, the increase in the free fraction will lead to increase in the drug's volume of distribution and plasma clearance, often resulting in clinically insignificant change in the drug's free fraction at steady state. Monitoring the free fraction of highly plasma protein bound drugs could be of value in patients with suspected drug interaction at distribution and with conditions of altered protein binding such as uremia and hypoalbuminemia. Unfortunately, free concentrations are not widely available, more expensive, and labor-intensive. Consulting a drug interaction resource when highly protein bound drugs are prescribed is recommended.

Metabolism and Excretion

Clearance

Disposition of drugs in the body occurs through metabolism to inactive metabolites, by excretion unchanged, or both. The main organ for metabolism is the liver; however, drug metabolism could happen in other sites such as the gastrointestinal (GI) tract, blood, and kidney. The main organ for drug excretion is the kidney; however, drug excretion could happen through other sites such as the GI tract and the lungs. Drug clearance is the volume of the blood cleared from the drug per unit time. Drug clearance depends on multiple factors such as drug metabolizing enzymes, protein binding, blood flow to the elimination organs and kidney and liver functions. Total clearance is the sum of the drug's renal and non-renal clearance. Appreciation of the renal and non-renal components of drug clearance (seen in drug monographs) are helpful in assessing the need for dosage adjustments in renal and/or hepatic impairment. To illustrate, as seen in Table 22.5, valproic acid is mainly metabolized with negligible portion of the dose is excreted unchanged by the kidney. Therefore, it is expected that dosage adjustment is not required in patients with renal failure but might be needed in patients with liver disease. On the other hand, vancomycin, digoxin and gabapentin are renally eliminated. Renal dosage adjustment of those drugs is recommended. In addition, to the route of drug elimination, clearance is an independent determinant of the drug half-life (see next section).

Table 22.5 Extent of metabolism and elimination of select drugs

Drug	Percent metabolism	Percent elimination	Half-life
Valproic acid	>93%	<7%	5–20 h
Digoxin	20%	80%	1–2 d
Vancomycin	Negligible	90%	8 h
Gabapentin	0%	100%	5–7 h

Half-Life

Drug half-life is the time taken for the drug concentration to be reduced into half. The value of the drug's half-life is dependent on the drug's clearance and volume of distribution. When the drug clearance increases with no V_d changes, half-life will shorten as the drug will be eliminated faster and vice versa. When the volume distribution increases with no clearance changes, the drug's half-life will increase. To simplify, drugs with large V_d are highly distributed in the body and are "hiding" in the tissues away from the elimination organs and thus have longer half-life. If both clearance and V_d change in the same direction, half-life is expected not to or mini-

mally change due to the counteracting effects of clearance and volume distribution.

Drug half-life corresponding to the patient's renal and liver function could be obtained from drug monographs and utilized in clinical decision-making. However, it is important to note that reported half-life values are based on population parameters and do not necessarily reflect the individual's half-life. In some situations, the drugs half-life for an individual can be calculated if two drug level values are available. Equation 22.2 depicts the simplest equation used to determine the elimination rate constant (k) for drugs with first order linear elimination kinetics, given that there is no dose administered between the two levels. C_1 is the first concentration, C_2 is the second concentration and t is the time interval in between. Then, half-life can be calculated using Eq. 22.3.

$$\ln C_1 - \ln C_2 = kt \tag{22.2}$$

$$t_{1/2} = \frac{0.693}{k} \tag{22.3}$$

Half-life is useful in day-to-day clinical practice. The value of the drug's half-life determines the time it takes for the drug to reach steady state. It generally takes three to five half-lives for the drug to reach steady state. For example, phenobarbital's half-life is 2–6 days. In other words, up to 3 weeks of phenobarbital administration are needed until it reaches a steady state. Drugs similar to phenobarbital will require a loading dose if rapid attainment of target levels is needed. In addition, it generally takes three to five half-lives for the drug to get eliminated from the system if it gets stopped. This is useful in situations where knowledge of the duration of the drug in the body is needed such as switching between agents with similar side effect profile and in cases of drug toxicity.

Pharmacokinetic Drug Interaction: Metabolism and Excretion

The most clinically significant pharmacokinetic drug interactions involve interactions at the metabolism and excretion levels. This could be due to co-administration with liver microsomal enzymes and/or P-glycoprotein inducers and inhibitors. Pharmacists need to check drug interaction references when implicated drugs are started, discontinued or their doses get changed due to their propensity of inhibiting, inducing liver microsomal enzymes or being substrates of liver microsomal enzymes. The following are examples of drugs commonly implicated in drug-drug interaction at the metabolism level:

- *Liver microsomal enzyme inducers*: rifampin, phenytoin, phenobarbital, primidone, carbamazepine, St. John's wort
- *Liver microsomal enzyme inhibitors*: clarithromycin, erythromycin, cimetidine, valproic acid, ketoconazole, ritonavir, voriconazole
- *P-glycoprotein inducers*: carbamazepine, rifampin, St. John's wort
- *P-glycoprotein inhibitors*: clarithromycin, erythromycin, amiodarone, ketoconazole
- *Drug classes prone to these kinds of interactions*: immunosuppressives, anticonvulsants, warfarin, direct oral anticoagulants, antiretrovirals, antifungals

Therapeutic Drug Monitoring: Rationale

Therapeutic drug monitoring (TDM) is the process of applying pharmacokinetic principles and knowledge of drug concentrations along with clinical assessment to facilitate appropriate dosing of drugs in order to maximize efficacy and minimize adverse drug reactions. The definition has three components. First, in order to conduct TDM, one should have a reasonable understanding of the main pharmacokinetic principles (discussed in the first part of this chapter). Second, blood concentration(s) of the drug monitored should be available. The third and most important component of the definition is clinical assessment such as patient characteristics, efficacy and toxicity of the drug and presence of drug interactions. Therapy adjustmnets merely based on drug concentrations, without clinical assessment, totally denies the benefit of TDM.

Generally, therapeutic drug monitoring is meant to improve patient outcomes by increasing the efficacy and minimizing toxicity. TDM is useful in those drugs with narrow therapeutic

range whose efficacy and toxicity are proportional to drug concentration. In other words, it is suitable for drugs that have well established reference range such as phenytoin and vancomycin. Additionally, TDM is useful in those drugs whose response cannot be assessed directly and at the same time there is a good correlation between drug concentration and response such as in the case of the antiepileptic and antirejection drugs. Furthermore, TDM is beneficial in those drugs with unpredictable pharmacokinetics with wide interpatient variability where administering the same dose to different individuals yields different drug concentrations and responses. For example, tacrolimus, an anti-rejection drug, has a wide inter-subject variability and its oral bioavailability ranges from 5% to 70%. Measuring tacrolimus level would be helpful in monitoring therapy in those patients. TDM could also be used in cases of suspected toxicity in drugs which exhibit concentration-dependent adverse reactions and toxicity as in the examples depicted in Table 22.6.

In some situation, measuring drug levels is the only way to predict pharmacokinetic drug-drug interactions. Examples of those interactions include the interaction between phenytoin and valproic acid and the interaction between tacrolimus and clarithromycin. When valproic acid is added to a drug regimen containing phenytoin therapy, it displaces phenytoin from protein binding increasing its unbound fraction. This results in increased phenytoin clearance and V_d. However, with chronic concomitant therapy, valproic acid inhibits phenytoin metabolism leading to another set of changes to phenytoin pharmacokinetics parameters. This complicated interaction on top of the nonlinear PK of phenytoin is an indication for monitoring the blood levels of phenytoin. Because valproic acid and phenytoin compete at the protein binding sites, measuring the free fraction of phenytoin, when available, could be more informative than the total level. Another example is clarithromycin interaction with tacrolimus. Clarithromycin, which is one of the most commonly prescribed antibiotics in the community, interferes with tacrolimus metabolism leading to a significant increase in tacrolimus concentrations, which could lead to tacrolimus-induced nephrotoxicity in transplant patients [3]. With the help of TDM, tacrolimus level will need to be monitored when clarithromycin has to be given to the patient. Another indication for TDM is in the conditions where altered pharmacokinetics of the drugs is expected such as in patients with liver or renal disease, in pregnancy, and in older adults. For example, gentamicin half-life increases by 35-fold in patients with renal failure, making the use of TDM very useful in those situations. On the other hand, TDM is not useful in drugs with linear predictable pharmacokinetics and drugs with wide therapeutic range. In addition, measuring drug lev-

Table 22.6 Concentration-dependent adverse reactions in select drugs

Drug	Concentration-dependent adverse reactions
Phenytoin	Nystagmus, dizziness, slurred speech, blurred vision, ataxia, ↓ mental status, confusion, coma
Vancomycin	Nephrotoxicity
Lithium	Tremors, muscle weakness, delirium, seizures, renal failure
Valproic acid	GI upset, tremors, thrombocytopenia, CNS depression, increased LFT, and serum ammonia
Digoxin	Nausea, vomiting, disorientation, bradycardia, hyperkalemia, arrhythmias
Tacrolimus	Neurotoxicity, nephrotoxicity
Theophylline	Nausea, vomiting, tremors, insomnia, arrhythmias, seizures, hyperthermia, brain damage
Voriconazole	Visual and auditory hallucinations

Table 22.7 Rationale of therapeutic drug monitoring (TDM)

TDM is useful	TDM is *not* useful
Drugs with well-established reference range Drug response cannot be assessed directly and there is a good correlation between drug concentration and response Drugs with narrow therapeutic window Drugs with unpredictable pharmacokinetics Suspected toxicity Compliance concerns Unpredictable drug interactions Disease-related altered pharmacokinetics	Predictable pharmacokinetics Pharmacological response not correlated with drug concentration Pharmacological response can be easily measured Wide therapeutic range

els is not needed in drugs where the pharmacological response is not correlated with drug concentration. Clopidogrel is an example where drug concentration is not correlated with the pharmacological response. The antiplatelet effect of clopidogrel persists beyond the presence of clopidogrel and its active metabolite. Measuring the platelet function will be more useful than measuring clopidogrel concentration. Furthermore, TDM is not of value if the drug's pharmacological response can be easily measured such as in the case of antihypertensives. Table 22.7 summarizes the rationale of therapeutic drug monitoring.

Exercise

You are the pharmacist in charge of the drug information center at a local hospital. The lab service manager contacted you to ask for your help. They are preparing a list of drug levels that might be needed for TDM. A preliminary list has been developed (Table 22.8), and he asks your help to review it.

Answer: Of the listed drugs in Table 22.8, TDM is of value in the following drugs: vancomycin, phenytoin, aminoglycosides, carbamazepine, tacrolimus, voriconazole, lithium, valproic acid, digoxin, and theophylline. Vancomycin trough level is a surrogate for area under the concentration time curve to minimum inhibitory concentration ratio (AUC/MIC), an efficacy marker and could be used to monitor its efficacy. Phenytoin exhibits nonlinear pharmacokinetics profile and have a wide interpatient variability in pharmacokinetics, and TDM might be useful. For aminoglycosides, which are concentration-dependent antimicrobials, TDM is useful for the aim of maximizing efficacy and minimizing adverse drug reaction. Carbamazepine induces its own metabolism and exhibits concentration-dependent adverse reactions. Tacrolimus, lithium, digoxin, and theophylline exhibit concentration-dependent adverse reactions, and TDM might be useful. In addition, tacrolimus has a wide interpatient variability in drug absorption adding more benefits to its TDM. For valproic acid, it exhibits concentration-dependent saturable protein binding and concentration-dependent adverse reactions, and TDM might be beneficial. Lastly, voriconazole undergoes nonlinear pharmacokinetics and its concentration might be related to its efficacy and adverse reactions. On the other hand, TDM is not of value in the following drugs: ciprofloxacin, ampicillin, lacosamide, levetiracetam, clopidogrel, vigabatrin, valsartan, and amlodipine. Ciprofloxacin and ampicillin have a wide therapeutic range and predictable kinetics. Similarly, lacosamide and levetiracetam have predictable linear pharmacokinetics. Clopidogrel and vigabatrin blood concentrations do not correlate with the pharmacological response and their levels are not useful. Lastly, valsartan and amlodipine have easily measurable drug response, the blood pressure.

Approach to Therapeutic Drug Monitoring

Pharmacists play an important role in therapy assessments using therapeutic drug monitoring. The following are the general TDM steps whenever a patient gets started on a drug where we have the capability of measuring its concentration:

- *Assessment if the drug is indicated and if it is a reasonable option for the patient*. For example, if the physician orders vancomycin for a patient, you do not need to adjust the dose or order level unless you confirm it is the right

Table 22.8 Therapeutic drug monitoring exercise: list of drugs

Vancomycin	Aminoglycosides	Ciprofloxacin	Ampicillin
Phenytoin	Carbamazepine	Lacosamide	Valproic acid
Levetiracetam	Tacrolimus	Voriconazole	Digoxin
Valsartan	Amlodipine	Lithium	Theophylline
Clopidogrel	Vigabatrin	–	–

antimicrobial for the patient or there is not another appropriate therapeutic alternative that does not need TDM.

- *Assessment of the appropriateness of initial dose of the drug*.
- *Determine if TDM of the selected drug is beneficial* (see previous section).
- *Assessment if a drug concentration monitoring is indicated*. This is a very important step. A drug level does not need to be measured just because we have the capability of measuring it. Drug concentrations shall be used a tool to assess patient's drug therapy rather than an ultimate goal to target (treat the patient, not the level). Measuring routine levels is not recommended. Drug levels are only measured if they are indicated. The following are the general indications for measuring a drug level:
  - Lack of efficacy
  - Suspected drug toxicity
  - Medication adherence concerns
  - Presence of unpredictable drug interactions
  - Drugs with nonlinear pharmacokinetics or wide interpatient variability
  - Presence of a superimposing comorbidity that might complicate the drug's pharmacokinetic profile, e.g., pregnancy
  - To determine the patient's "therapeutic" drug concentration.
- *Determine the timing of the drug level withdrawal*. Drug levels are generally measured at steady state (3–5 drug half-lives). However, pre-steady-state levels can be beneficial in some situations to determine the adequacy of the dosage. With regard to the timing related to the dose, generally trough levels are recommended. However, for some drugs peak levels might be needed such as in the case of conventional dosing of aminoglycosides. Always check drug-specific TDM information to determine the appropriate timing of the drug concentration.
- *Assessment of the drug level in the context of the patient's clinical picture*. This allows determining if dose alteration is needed.

Clinical Pearls

- Pharmacokinetic concepts are essential in day-to-day clinical practice.
- Bioavailability, salt factor and rate of drug absorption help in determining the equivalent dosage in formulation conversions.
- Volume of distribution reflects drug distribution in the body and is helpful in determining the loading dose of the drug.
- Total clearance is the sum of the drug's renal and non-renal clearance. Appreciation of the renal and non-renal components of drug clearance is helpful in assessing the need for dosage adjustments in renal and/or hepatic impairment.
- Knowledge of the drug half-life helps determine the time it takes for the drug to reach steady state and the time it takes to get out from the system.
- TDM is an important therapeutic tool in disease management. If used for the right drug, the right time and when needed, TDM will be a powerful tool to optimize medication therapy.

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Liver Function Assessment

23

Mohamed A. Omar

Chapter Objectives

1. Understand the different types of liver diseases
2. Interpret and understand the significance of liver chemistry tests
3. Interpret and utilize the different scoring systems to assess hepatic function
4. Assess drug-induced liver injury and differentiate between its different types

Background

The liver is the largest organ of the body and it performs a multitude of complex functions that helps in maintaining homeostasis and health. The liver receives its blood supply from two different sources. It receives oxygen-rich blood via the hepatic artery and receives nutrient-rich blood via the portal vein arising from the stomach, intestine, pancreas, and spleen. Hepatocytes constitute the majority of the cells in the liver, and they are involved in carrying out the different functions of the liver. These include synthesis of serum proteins (such as albumin and coagulation factors), regulation of metabolism (glucose, lipids, amino acids, and cholesterol), and biotransformation and detoxification of endogenous as well as exogenous compounds including drugs [1]. This array of functions performed by the liver makes it more complicated to measure the function of the liver. There is no one test available that can provide an assessment of the liver's total functional capacity. Thus, the diagnosis and assessment of liver function and disease involves a detailed examination of the patient's clinical history, physical examination, imaging, as well as patterns of abnormalities in laboratory tests of liver injury and function. This chapter aims to help the pharmacist to have an assessment of the patient's liver function and to investigate possible drug-induced causes of liver disease as well as manage drug therapy in patients with existing liver disease.

Liver Diseases

There are many causes for liver diseases and they can manifest in different ways. They can be classified clinically into three broad categories [1]:

- *Hepatocellular:* This mainly involves damage to the hepatocytes. Examples of the common causes of hepatocellular injury include acute viral hepatitis and alcoholic liver disease.
- *Cholestatic:* This mainly involves inhibition of bile flow which can result from intrahepatic or extrahepatic cholestasis. Intrahepatic cholestasis involves a dysfunction in the

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secretion of bile by the hepatocytes as well as diseases involving the bile ducts within the liver. Extrahepatic cholestasis involves the obstruction of the bile ducts outside the liver which can happen due to several reasons such as gall stones, primary sclerosing cholangitis, pancreatitis, and tumors [2].

- *Mixed:* It mainly features both hepatocellular and cholestatic injury. This includes many drug-induced liver diseases and viral hepatitis.

Liver Chemistry Tests

Due to the multitude of physiological functions that the liver performs, there is no one single test that can be utilized to assess total liver function. However, utilizing a panel of liver tests that can measure some of the functions carried out by the liver or detect liver damage can provide information on the presence of liver disease, type of liver disease, extent of liver damage, as well as response to treatment. At most healthcare facilities, liver chemistry tests can be ordered as a panel referred to as *LFT panel* or *LFTs* (liver function tests). This naming can be misleading as not all the liver chemistry tests included actually measure the "liver function". *LFTs* usually consist of the aminotransferases including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) as well as bilirubin and albumin. Table 23.1 separates liver chemistry tests into four broad categories based on the hepatic process they assess.

Table 23.1 Categories of liver chemistry tests by the hepatic process [2]

Hepatic process	Liver chemistry test
Synthetic function	Albumin Prealbumin PT/INR
Cholestasis	Bilirubin ALP GGT 5′-nucleotidase
Hepatocellular injury	ALT AST
Detoxification	Ammonia

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *GGT* Gamma-Glutamyl Transferase, *INR* international normalized ratio, *PT* prothrombin time

It is important to note that an abnormal *LFT* usually means a value exceeding the upper reference limit which can vary among laboratories. It is common practice to define the normal range as mean value ±2 standard deviations of the values observed in the reference normal population. Thus, abnormal aminotransferase levels can be observed in the normal population and patients with chronic liver diseases can sometimes present with normal aminotransferases levels [2–5].

Liver Synthetic Function Tests

One of the main functions of the liver is the biosynthesis of various proteins, notably albumin and the clotting factors. The measurement of the levels of these proteins can provide an assessment of the biosynthetic function of the liver. However, these tests are usually not sensitive enough to detect lower levels of liver injury or dysfunction as the liver has a high functional reserve. This means that the liver can maintain normal levels of its biosynthetic function despite having a significant damage. Inadequate synthetic function is usually observed in hepatic cirrhosis or massive liver injury. In these situations, these tests are very useful in determining prognosis and recovery.

Albumin

Albumin is a major plasma protein that is synthesized exclusively by hepatocytes. It functions to maintain plasma oncotic pressure and it binds and transports various molecules including drugs, hormones, and waste products such as bilirubin. Albumin normal range is 40–50 g/L and it has a relatively long serum half-life of ≈ 19–21 days [6]. Therefore, the decline in serum albumen following the onset of liver damage is generally slow. Thus, albumin levels are generally in the low side in patients with chronic cirrhosis but are usually within normal limits in patients with acute hepatic dysfunction due to acute viral hepatitis or drug-induced hepatic injury [2].

In addition, albumin levels can be reduced in other clinical scenarios irrespective of liver disease. These include malnutrition or malabsorption, chronic kidney disease, severe burns, increased blood volume, and systemic inflammation. Hospitalized patients who are acutely ill usually have low albumin levels due to a combination of systemic inflammation, malnutrition, and IV fluid administration. A low albumin level together with no alterations in other liver tests or a clinical evidence of liver disease is usually indicative of a non-hepatic cause for hypoalbuminemia. On the other hand, in patients with known cirrhosis and decreased albumin levels, monitoring of albumin can help with assessing the prognosis of the case [3].

Another important aspect that is important for pharmacists to consider is that hypoalbuminemia will affect the pharmacokinetics of highly protein-bound drugs. Lower albumin levels will result in higher proportion of free drug which could potentially result into increased activity or increased side effects. A common example is phenytoin, where it is recommended to use the free phenytoin level rather than the total phenytoin levels for therapeutic drug monitoring in patients with low albumin levels.

Prealbumin

Prealbumin is another plasma protein closely related to albumin. As compared to albumin, it has a shorter serum half-life of ≈ 2 days and is more sensitive to protein nutrition and less sensitive to hepatic function or fluid status [7]. It is mainly utilized clinically to assess the nutritional status of acutely ill hospitalized patients.

Prothrombin Time (PT) / International Normalized Ratio (INR)

All the blood clotting factors are synthesized exclusively by the hepatocytes with the exception of factor VIII which is synthesized by the vascular endothelial cells. Compared to albumin, the half-lives of the clotting factors are much shorter ranging from 6 h to 5 days which makes measuring them a good indicator for hepatic synthetic function during acute hepatic dysfunction. However, the liver has a great synthetic reserve and the levels of blood clotting factors will decrease only due to substantial hepatic impairment (>80% of the synthetic capability) [2].

Serum prothrombin time (PT) measures the activity of factors II, V, VII, and X which are produced by the hepatocytes and require vitamin K for their activation. The international normalized ratio (INR) is a standardized index that standardizes PT taking into account the differences in test reagents used at different laboratories. INR/PT values are elevated when there are reduced circulating levels of these factors or their activation is impaired. Thus, impaired hepatic synthesis, vitamin K deficiency, or using vitamin K antagonists (such as warfarin) will result in elevated PT/INR. Response to vitamin K administration can be used as a tool to examine the etiology of prolonged PT/INR. Elevated PT/INR due to vitamin K antagonists, malabsorption, or antibiotic-induced disturbance in gut flora will respond well to vitamin K, while vitamin K is not effective in the case of hepatic synthetic dysfunction.

Liver Tests that Reflect Cholestasis

These are tests that look at the excretory function of the liver. They include bilirubin, alkaline phosphatase (ALP), 5′- nucleotidase, and γ-glutamyl transpeptidase (GGT). These tests can help differentiate between hepatocellular and cholestatic liver diseases, but they cannot distinguish between intrahepatic and extrahepatic cholestasis. This is usually diagnosed by diagnostic imaging as extrahepatic cholestasis is usually associated with dilation of the bile ducts.

Bilirubin

Bilirubin is the breakdown product of heme-containing proteins, most important of which is hemoglobin in red blood cells. Bilirubin is present in the blood as conjugated (direct) and unconjugated (indirect) bilirubin. Unconjugated bilirubin is lipophilic and is bound to albumin in the blood, while conjugated bilirubin is water soluble and it can be excreted in the bile as well as by the kidneys. Jaundice, also known as icterus, results from elevated bilirubin in the

blood. It manifests as yellow discoloration of the skin and sclera of the eye [2].

In patients with elevated bilirubin, it is important to identify if only unconjugated bilirubin is elevated or both fractions are elevated. Isolated increase in unconjugated bilirubin (more than 70% unconjugated) is seen most commonly in hemolytic disorders or due to some genetic conditions such as Gilbert's syndrome and is rarely due to liver disease [8]. Hemolytic disorders result in excessive destruction of red blood cells leading to increased production of unconjugated bilirubin exceeding the capacity of the liver to conjugate and excrete bilirubin leading to hyperbilirubinemia. On the other hand, conjugated hyperbilirubinemia (more than 50% conjugated bilirubin) usually results from liver or biliary tract disease. Elevation of conjugated bilirubin can happen in any type of liver disease, while isolated elevation in unconjugated bilirubin usually refers to a non-hepatic cause.

Bilirubin can also be measured in the urine. Unconjugated bilirubin is usually albumin-bound and is not cleared by the kidney, while conjugated bilirubin is water-soluble and can be filtered by the kidney [8]. A urine dipstick to test for bilirubin in the urine can be used as an alternative to fractionation of serum bilirubin. The presence of bilirubinuria usually implies the presence of liver disease [8].

Alkaline Phosphatase (ALP), 5′-Nucleotidase, γ-Glutamyl Transpeptidase (GGT)

Alkaline phosphatase (ALP) is found in various body tissues, mainly in the liver, bone, small intestine, and placenta. ALP levels can be higher in children (up to three times the adult range) due to bone growth. Also, ALP can be elevated during late pregnancy as a result of increased placental ALP. Other than that, elevated ALP is usually correlated clinically with cholestatic liver disease. An increase in ALP levels of more than four times the normal range usually suggests a cholestatic disorder, while levels of three times normal or less can occur in any type of liver disease.

ALP can also be elevated due to non-hepatic causes which include bone disorders (Paget disease, healing fractures, osteoporosis, rickets, osteomalacia, hypervitaminosis D, or vitamin D deficiency), diabetes mellitus, renal failure, sepsis, neoplasms, hyperparathyroidism, and hyperthyroidism [2]. One practical approach to identify if the liver is the source of the elevated ALP is to measure serum 5′-nucleotidase or GGT. If they are elevated, then it is highly likely that the elevated ALP is due to a liver disorder [8]. These enzymes are rarely elevated in non-hepatic disorders. In addition, GGT usually is elevated in alcoholic liver disease where a GGT/ALP ratio >2.5 usually refers to alcohol abuse [2].

Liver Tests that Reflect Hepatocellular Injury

Aminotransferases (ALT and AST)

Aminotransferases (also known as transaminases) are sensitive indicators of hepatocyte injury and thus are very useful in identifying acute hepatic diseases such as hepatitis [8]. They include aspartate aminotransferase (AST), also known as serum glutamic oxaloacetic transaminase (SGOT), as well as alanine aminotransferase (ALT), also known as serum glutamic-pyruvic transaminase (SGPT). These enzymes are primarily located inside the hepatocytes and are released into the serum when the hepatocytes are damaged. Aminotransferase levels are very sensitive and are elevated even with minor hepatocyte injury. Small increases (up to 300 IU/L) are nonspecific and can occur with minor liver disorders, while marked elevations (more than 1000 IU/L) are usually a marker of extensive hepatocellular injury which usually occur due to viral hepatitis, ischemic hepatitis, or drug-induced liver injury [8]. However, aminotransferase levels provide no prognostic benefit in acute liver disease.

The ratio of AST to ALT can provide valuable diagnostic information. Alcoholic liver diseases are usually characterized by an AST:ALT ratio of more than 2. This is mainly due to low ALT levels due to alcohol-induced deficiency of pyridoxal phosphate [8].

Tests Reflecting Detoxification

Ammonia

Ammonia is primarily produced in the body during normal protein metabolism as well as by bacterial catabolism of proteins in the colon. Ammonia is mainly detoxified in the liver (converted into urea) and the muscles (binds to glutamic acid to form glutamine). Therefore, patients with advanced liver disease or muscle wasting can develop hyperammonemia [9]. Ammonia possibly plays a role in development of hepatic encephalopathy which is a group of neuropsychiatric symptoms ranging from changes in personality to coma. Increased ammonia in the blood together with increased permeability of the blood-brain barrier to ammonia, commonly seen in patients with hepatic encephalopathy, results in ammonia crossing the blood-brain barrier and inducing brain edema [2, 9]. However, ammonia levels do not correlate well with hepatic encephalopathy in patients with chronic liver failure and the diagnosis of hepatic encephalopathy relies more on the patient's history and clinical evaluation [2].

In addition, ammonia levels can be elevated as a result of medications (most commonly valproic acid), urea cycle disorders, Reye syndrome, and infections with ammonia producing bacteria (such as mycoplasma) [2, 10].

Patterns of Liver Tests Abnormalities

The liver has a complicated physiological role and performs a multitude of physiological functions. There is no one test that can provide an assessment of the overall liver function; however, each one of the tests mentioned in the previous sections assesses a certain aspect of the liver's function and status. Thus, it is important not to look at the results of any of the liver tests in isolation of the clinical picture, the results of other relevant tests, or the results of diagnostic imaging. By looking at the pattern of the different liver tests in tandem, one can determine the general category of liver disease. Table 23.2 depicts various patterns of liver tests associated with the different classes of liver diseases.

Table 23.2 Patterns of liver tests associated with the different classes of liver diseases [1]

Liver disorder	Bilirubin	Aminotransferases (ALT, AST)	ALP	Albumin	PT/INR
Acute hepatocellular disease (viral, drug-induced, or ischemic hepatitis)	Both fractions (conjugated and unconjugated) elevated Bilirubinuria	Both ALT and AST elevated (>1000 IU/L) ALT > AST	Normal or mild elevation (<3 times normal)	Normal	Usually normal Poor prognosis if elevated (more than 5 times normal) and not corrected by vitamin K
Chronic hepatocellular disease	Both fractions elevated Bilirubinuria	Mild elevation (<300 IU/L)	Normal or mild elevation (< 3 times normal).	Decreased	Prolonged Not corrected by vitamin K
Alcoholic hepatitis	Both fractions elevated Bilirubinuria	AST:ALT >2	Normal or mild elevation (<3 times normal)	Decreased.	Prolonged Not corrected by vitamin K
Hepatic cholestasis	Both fractions elevated Bilirubinuria	Normal or mild elevation (<300 IU/L)	Highly elevated (>4 times normal)	Normal unless chronic condition	Normal If prolonged will respond to vitamin K
Hemolytic disorders	Increased unconjugated fraction No Bilirubinuria	Normal	Normal	Normal	Normal

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *GGT* gamma-glutamyl transferase, *INR* international normalized ratio, *PT* prothrombin time

Other Liver Assessment Tests

Liver laboratory tests can provide a general category of liver disease. Additional tests are usually required to make the proper specific diagnosis and to assess the severity of disease. These include:

- *Liver ultrasound:* important in distinguishing between intrahepatic and extrahepatic cholestasis
- *Percutaneous liver biopsy*: important for assessing hepatic fibrosis which helps to identify the severity and stage of liver disease (early, advanced, precirrhotic, or cirrhotic)
- *Noninvasive tests to detect hepatic fibrosis*: these include transient elastography and magnetic resonance elastography [8]
- *Tests for viral hepatitis*: These include serologic tests for antibodies and molecular assays to detect viral genetic material. These tests together with the clinical history, epidemiology, and patient risk factors can help provide a correct diagnosis for viral hepatitis and distinguish between the different hepatitis viruses (Hepatitis A, B, C, D, or E) [2].

Scoring Systems of Liver Diseases

Liver cirrhosis is associated with high rates of mortality and morbidity, and the 1-year mortality rate ranges widely from 1% to 57% based on the stage of hepatic cirrhosis and the complications associated with it [11]. This highlights the importance of identifying patients at high risk. Liver biopsy is the most accurate way to assess the severity and stage of hepatic cirrhosis. However, cirrhosis can also be staged clinically by using the Child-Turcotte-Pugh classification (also referred to as Child-Pugh score or CTP score). Table 23.3 shows the details of CTP score criteria. CTP score is a good predictor of prognosis in hepatic cirrhosis and can provide guidance to identify patients eligible for liver transplant. In addition, it is usually used to guide drug dosing adjustment in patients with liver cirrhosis.

Table 23.3 Child-Turcotte-Pugh (CTP) score [11]

	1	2	3
Encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)
Ascites	None	Mild	Moderate-refractory
Albumin (g/L)	>35	28–35	<28
Bilirubin (umol/L)	<34	34–50	>50
INR	<1.7	1.7–2.3	>2.3

Class A (Mild): ≤6; Class B (Moderate): 7–9; Class C (Severe): ≥10

Table 23.4 Three-month mortality based on MELD and CTP scores [13]

		3-month Mortality %
MELD score	<9	1.9
	10–19	6.0
	20–29	19.6
	30–39	52.6
	>40	71.3
CTP score	<7–9	4.3
	10–12	11.2
	13–15	40.1

CTP Child-Turcotte-Pugh (CTP) score, *MELD* Model for end-stage liver disease

Model for end-stage liver disease (MELD) is another scoring system that currently replaced Child-Pugh score for identifying liver transplant candidates. It incorporates only three noninvasive variables: INR, serum bilirubin level, and serum creatinine concentration [11]. It uses a linear regression mathematical equation involving these three variables to provide a numerical value that correlates with mortality from liver disease [12]. The higher the MELD score, the higher the mortality and morbidity [13]. Table 23.4 depicts the correlation of mortality rates with CTP and MELD scores [13].

Drug-Induced Liver Injury

The liver plays a major role in detoxifying and eliminating drugs and at the same time is susceptible to toxicity due to exposure to medications. Over one thousand medications, herbal supplements, illicit drugs, and chemicals can induce

hepatotoxicity [14]. The incidence of drug-induced liver injury (DILI) has been increasing, and it is the main reason for post-marketing drug withdrawals [14]. Most cases of DILI recover completely with no residual damage or injury. However, the rare cases that progress into developing acute liver failure, chronic liver injury, and cirrhosis or to developing vanishing bile duct syndrome (chronic cholestasis and loss of intrahepatic bile ducts) can result into death or requirement of liver transplantation [15].

Adults are generally more likely to develop DILI as compared to children, and women are at higher risk than men. Other factors that can increase risk of DILI include obesity, malnutrition, pregnancy, concurrent medications, genetic susceptibility, and a history of drug reactions [16]. Preexisting liver diseases and other comorbidities do not affect the risk of developing DILI as much as they affect the ability of the patient to recover from DILI [17].

Types of DILI

DILI can be either due to direct toxic effects or can be idiosyncratic. Idiosyncratic drug-induced hepatotoxicity is generally more predominant, while only few agents can induce direct hepatotoxicity (e.g., acetaminophen and methotrexate) [14].

Direct Toxic

Direct toxic drug-induced hepatotoxicity is generally predictable and dose-related and usually occur within a short time period after exposure. In addition, direct hepatotoxins usually produce distinct morphological abnormalities that are reproducible and characteristic of each toxin [16, 18].

Idiosyncratic

On the other hand, idiosyncratic drug-induced hepatotoxicity is usually unpredictable and dose-independent and can occur within a few days up to 12 months after exposure. Unlike direct hepatotoxins, extrahepatic manifestations such as arthralgia, fever, rash, leukocytosis, and eosinophilia can occur in about one quarter of patients with idiosyncratic drug-induced hepatotoxicity [18].

Patterns of Liver Enzyme Changes in DILI

Similar to general liver diseases, DILI can be categorized based on the changes in liver enzymes into hepatocellular, cholestatic, or mixed disease [19].

Hepatocellular Injury

DILI due to hepatocellular injury is usually characterized by marked elevations in ALT and AST which usually precedes elevations in total bilirubin and associated with modest increase in ALP levels [16]. Hepatocellular injury is defined by the US Food and Drug Administration as an increase in ALT of at least 3 times above the upper limit of normal (ULN) together with a rise in total bilirubin of at least 2 times above ULN and R >5 [19]. Where R is defined as in Eq. 23.1.

$$R = \left(\text{Measured ALT} / \text{ULN of ALT}\right) \div \left(\text{Measured ALP} / \text{ULN of ALP}\right). \quad (23.1)$$

Common examples of DILI due to hepatocellular injury is toxicity due to isoniazid and acetaminophen.

Cholestatic Injury

Cholestatic injury is characterized by an increase in ALP level that precedes or is more prominent than increases in ALT or AST [16]. It is defined as ALP >3 times above ULN and total bilirubin above 2 times ULN and R less than or equal 2. This injury can be caused by medications like erythromycin, carbamazepine, or amoxicillin-clavulinic acid [19].

Mixed Injury

In this kind of injury, both ALT and ALP are elevated and R ranges from 3 to 4. Medications such as phenytoin, phenobarbital, and sulfonamides could cause mixed injury [16, 19].

Diagnosis of DILI

The clinical symptoms and signs as well as the patterns of liver test abnormalities in DILI can be difficult to distinguish from other forms of liver diseases. There is no specific clinical, laboratory,

or histological feature that can definitely diagnose DILI [20]. The diagnosis of DILI is more of a diagnosis of exclusion that relies on clinical judgement, potential of the agent in question to cause liver injury as compared to other causes of liver injury, and liver test abnormalities. It is important to consider the following six factors in DILI diagnosis [15]:

1. Time to onset
2. Time to recovery
3. Injury pattern (hepatocellular, cholestatic, or mixed)
4. Exclusion of other causes of liver injury
5. If the drug in question is reported to induce liver injury
6. Response to reexposure

Because of these multiple factors, the diagnosis of DILI can be complicated, and identifying causality can be debatable. A number of tools have been developed to standardize the assessment of causality [15]. These include:

- *Roussel Uclaf Causality Assessment Method (RUCAM) scale:* specifically developed for assessment of DILI and include liver specific criteria including risk factors and use of other hepatotoxic drugs [21]. Despite its complexity, RUCAM scale remains the most widely used and studied tool to assess causality in DILI [20]. See Table 23.5 for details of RUCAM scale.
- *Maria and Victorino (M & V) Scale:* a modification of the RUCAM scale meant to simplify it and to improve its usability [22].

Table 23.5 RUCAM Scale to assess causality for DILI

	Hepatocellular type		**Cholestatic or mixed type**		**Assessment**
1. Time to onset	**Initial treatment**	**Subsequent treatment**	**Initial treatment**	**Subsequent treatment**	**Score**
From the beginning of the drug:					
Suggestive	5–90 days	1–15 days	5–90 days	1–90 days	+2
Compatible	<5 or > 90 days	>15 days	<5 or >90 days	>90 days	+1
From cessation of the drug:					
Compatible	≤15 days	≤15 days	≤30 days	≤30 days	+1
If reaction occurred before starting the drug or ≥15 days (hepatocellular) or ≥30 days (cholestatic) after stopping, the injury should be considered unrelated and RUCAM cannot be calculated					
2. Course	**Change in ALT between peak value and ULN**		**Change in ALP (or total bilirubin) between peak value and ULN**		**Score**
After stopping the drug:					
Highly suggestive	Decrease ≥50% within 8 days		Not applicable		+3
Suggestive	Decrease ≥50% within 30 days		Decrease ≥50% within 180 days		+2
Compatible	Not applicable		Decrease <50% within 180 days		+1
Inconclusive	No information or decrease ≥50% after 30 days		Persistence or increase or no information		0
Against the role of the drug	Decrease <50% after 30 days OR recurrent increase		Not applicable		−2
If the drug is continued:					
Inconclusive	All situations		All situations		0
3. Risk factors					**Score**
Alcohol or pregnancy	Alcohol: Present Absent		Alcohol or pregnancy: Present Absent		+1 0
Age	Age of the patient: ≥55 years <55 years				+1 0
4. Concomitant drugs					**Score**
None or no information or concomitant drug with incompatible time to onset					0
Concomitant drug with suggestive or compatible time to onset					−1
Concomitant drug known to be hepatoxic with a suggestive time to onset					−2
Concomitant drug with clear evidence for its role (positive rechallenge or clear link to injury and typical signature)					−3

Table 23.5 (continued)

	Hepatocellular type	Cholestatic or mixed type	Assessment
5. Exclusion of other causes of liver injury			**Score**
Group I (6 causes): Acute viral hepatitis due to HAV, HBV, or HCV, biliary obstruction, alcoholism, recent history of hypotension, shock or ischemia *Group II:* Complications of underlying liver disease(s), or clinical features or serologic and virologic tests indicating acute CMV, EBV, or HSV infection.		All causes in group I and II ruled out	+2
		The 6 causes of group I ruled out	+1
		Five or 4 causes of group I ruled out	0
		Less than 4 causes of group 1 ruled out	−2
		Nondrug cause highly probable	−3
6. Previous information on hepatotoxicity of the drug:			**Score**
Reaction labeled in the product characteristics			+2
Reaction published but unlabeled			+1
Reaction unknown			0
7. Response to readministration:			**Score**
Positive	Doubling of ALT with drug alone	Doubling of ALP (or bilirubin) with drug alone	+3
Compatible	Doubling of the ALT with the suspect drug combined with another drug which had been given at the time of onset of the initial injury	Doubling of the ALP (or bilirubin) with the suspect drug combined with another drug which had been given at the time of onset of the initial injury	+1
Negative	Increase of ALT but less than ULN with drug alone	Increase of ALP (or bilirubin) but less than ULN with drug alone	−2
Not done or not interpretable	Other situations	Other situations	0

Roussel Uclaf Causality Assessment Method (RUCAM) score <3 (unlikely), 4–5 (possible), 6–8 (probable), and >8 (highly probable). (Adapted from LiverTox.nih.gov [15])

- *Naranjo Probability Scale:* not specific to DILI and can be used to assess any potential drug-related adverse effect [23] (see Chap. 2).

Dosage Adjustment in Liver Diseases

As the liver has a wide range of physiological functions, liver impairment can have a significant impact on various aspects of drug pharmacokinetics. Unfortunately, there is no single laboratory test that can measure the overall liver function in the same way creatinine clearance is used to assess renal function [24]. In patients with acute hepatitis, there is a mild or transient decrease in liver drug metabolism that usually does not necessitate dosage adjustment. On the other hand, patients with liver cirrhosis, the permanent loss of hepatocyte function necessitates dosage adjustment for hepatically metabolized drugs [24]. CTP score can be used to guide drug dosing in patients with liver cirrhosis. Some drug monographs will provide dosing guidance based on CTP scores. In general, for drugs that are primarily metabolized by the liver (>60%) it is appropriate to moderately decrease the initial dose (~25%) for a CTP score of 8–9, and to decrease the initial dose further for CTP score of 10 or greater (~50%) [24].

Oral drug absorption can be also impacted as hepatic dysfunction can result in decreased first pass metabolism resulting in increased bioavailability of oral drugs affected by first-pass metabolism [24]. In addition, decreased plasma albumin in patients with liver disease can significantly affect highly protein-bound drugs. The decreased albumin can result in an increased free fraction of the drug which has to be taken into account during dose adjustments. It is also important to account for the increased volume of distribution in patients with significant ascites. Water soluble medications such as beta lactams might require a higher loading dose to account for the increased volume.

For medications where there is no clear recommendation for drug dosing in hepatic dysfunction, the pharmacist can utilize their understanding of the drug's pharmacokinetics and the availability of alternatives to guide their decision. These principles include:

- Change to a therapeutic alternative not affected by the liver function
- Decrease initial dose, which can be guided by CTP score
- Titrate dose slowly with close monitoring of therapeutic response and adverse effects
- Close therapeutic drug monitoring, if available

Clinical Pearls

- The liver performs a wide array of physiological functions and there is no single test to assess its overall function
- Assessment of patients with liver disease requires incorporating an understanding of the different liver chemistry tests with the patients' overall clinical picture and other investigations.
- Diagnosis of drug-induced liver disease is a diagnosis of exclusion. The pharmacist has to take many factors into consideration to assess causality.
- Hepatic dysfunction can significantly impair various aspects of drug pharmacokinetics which necessitates close monitoring by the pharmacist.

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Kidney Function Assessment

24

Rene R. Breault

Chapter Objectives

1. Describe basic kidney physiology and function.
2. Explain the definitions of acute kidney injury (AKI) and chronic kidney disease (CKD).
3. Describe the risk factors for both chronic kidney disease (CKD) and acute kidney injury (AKI).
4. Apply a systematic approach to assessing patients' kidney function.
5. Interpret the various laboratory tests used to assess kidney function.

Background

Kidney disease affects 1 in 10 Canadians with millions more at risk [1]. Worldwide, approximately 10% of the population is affected by chronic kidney disease (CKD) [2]. A significant proportion of individuals may go unrecognized and therefore not receive timely treatment to delay progression of their kidney dysfunction. Pharmacists are in an ideal position to be able to help screen and assess patients who may be at risk of CKD or AKI. Research has shown that targeted screening by pharmacists can help identify patients with CKD, which may have important implications for prevention and management of the disease [3]. Assessing kidney function is an important skill not only for determining the appropriateness of drug dosages but also to help with ongoing monitoring and management of kidney disease.

The kidneys are responsible for the following functions [4]:

1. Regulation of fluid volume, osmolarity, blood pressure, electrolyte concentrations, and acidity
2. Excretion of metabolic end products and foreign substances such as urea, toxins, and drugs
3. Synthesis of renin, erythropoietin, and calcitriol (vitamin D3)

The kidneys receive their blood supply from the renal arteries and receive about 20% of the cardiac output under normal resting conditions [5]. The functional unit of the kidney is the nephron, and each kidney contains approximately one million of these microscopic subunits, which work to filter the blood and produce urine [5]. Three exchange processes occur within the nephrons: (1) glomerular filtration, (2) tubular reabsorption, and (3) tubular secretion. When the kidneys begin to fail due to acute injury/toxicity

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or chronic disease, these exchange processes can become impaired, and if undetected or untreated, can progress to impede the regulatory, excretory and synthetic functions of the kidney.

Approach to Assessing Renal Function

Assessment of renal function involves the following key steps:

1. Obtain patient clinical history (medical/medication history, signs, and symptoms) and demographic information to determine if they are at risk for renal dysfunction.
2. Obtain relevant laboratory data in order to assess markers of renal function.
3. Determine if the patient has acute kidney injury (AKI) or chronic kidney disease (CKD) according to guideline definitions.
4. Ensure appropriate therapies are in place to manage the renal dysfunction (AKI or CKD).
5. Discontinue any nephrotoxic drugs (AKI) and/or adjust drug dosages (CKD).
6. Provide ongoing monitoring and assessment of renal function and potential associated complications.

Markers of Kidney Function

Glomerular filtration rate (GFR) cannot be measured directly. An ideal marker of kidney function should be at stable concentration in plasma, physiologically inert, freely filtered at the glomerulus, not secreted, reabsorbed, synthesized, nor metabolized in the kidney; and the amount secreted at the glomerulus is equal to the amount excreted in the urine.

Exogenous and Endogenous Markers

Table 24.1 lists the various exogenous and endogenous markers used to assess kidney function. These methods are generally used for research purposes and are typically not used in clinical practice except in circumstances when specific patient factors may render traditional methods of assessment such as serum creatinine unreliable or inaccurate. Their invasiveness and cost also prohibit their widespread use in everyday practice.

Serum creatinine (SCr) and BUN are the most commonly used markers to assess renal function. SCr is used to estimate glomerular filtration rate and to calculate creatinine clearance for the purpose of drug dosage adjustments in renal impairment. Both BUN and SCr can be used to assess patients with acute kidney injury and chronic kidney disease, which will be discussed later in the chapter. Proteinuria (protein in the urine) is also used to screen for and monitor progression of chronic kidney disease.

Serum Creatinine (Reference Range 50–110 µmol/L)

Creatinine is a nonprotein, nitrogenous, metabolic by-product of the muscles, which under normal physiologic conditions remains constant if muscle mass is not significantly changed. It is mostly eliminated by glomerular filtration, and at steady state, the rate of creatinine production equals its excretion. Although there is an inverse relationship between SCr and kidney function, it should not be the only method for evaluation of renal function as there are a number of factors that can affect SCr concentrations (Table 24.2).

Table 24.1 Markers of kidney function

Exogenous markers	Endogenous markers
Inulin Iothalamate Cr-EDTA (ethylenediamine tetra-acetic)	Cystatin C

Table 24.2 Factors affecting serum creatinine concentration (SCr)

Decreased SCr	Increased SCr
Paralysis, low activity level Elderly Decreased muscle mass Cirrhosis	Renal impairment Large dietary protein intake Vigorous exercise Increased muscle mass

Creatinine clearance (CrCl) can be measured using a 24-hour or timed urine collection to estimate a patient's renal function. This method is often difficult to implement and prone to errors in collection but can be useful in specific patients. It is more common to use the measured SCr to calculate an estimate of a patient's renal function. The most utilized equation is the Cockcroft-Gault formula (Eq. 24.1) [6]. The formula uses the patient's age and body weight, in addition to the SCr:

$$\mathrm{CrCl}\left(\mathrm{ml/min}\right)=\frac{\left(140-\mathrm{Age}\right)\times\mathrm{Weight}\left(\mathrm{kg}\right)}{SCr\left(\mu\mathrm{mol/L}\right)}\times 1.2\left(\mathrm{males}\right) \tag{24.1}$$

There has been debate in recent years as to which weight to use in the formula, with weight-adjusted and nonweight-based formulas being developed in attempts to improve the accuracy of the equation. Using total body weight in an overweight individual may overestimate renal function and conversely underestimate renal function in an underweight person. Some clinicians use an adjusted or ideal body weight in these individuals in hopes that this may provide a more accurate estimate of creatinine clearance. It should also be noted that this formula should only be used in patients with a SCr at steady state, and it will not be of clinical value in patients with acute kidney injury or on dialysis. Creatinine clearance as calculated by the Cockcroft-Gault equation has been used to determine dosages for many medications that are renally excreted, and there are many resources available to pharmacists to determine drug dosages based on renal function.

Equations to estimate GFR include the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas [7, 8]. These formulas are used to determine staging of chronic kidney disease due to their improved predictive performance over the Cockcroft-Gault equation. It has also been suggested that they be incorporated into drug monographs to provide dosage recommendations for patients with renal dysfunction. Many laboratories now report an estimated GFR with the measured SCr using one of the aforementioned equations.

$$\mathrm{GFR}\left(\mathrm{ml/min/1.73m^2}\right)=175\times\left(\frac{SCr}{88.4}\right)^{-1.154}\times\left(\mathrm{Age}\right)^{-0.203}\times\left(0.742\,\mathrm{if\ female}\right)\times\left(1.212\,\mathrm{if\ African\ American}\right)$$

Where:
SCr is serum creatinine in μmol/L,

$$\mathrm{MDRD} \tag{24.2}$$

$$\mathrm{GFR}\left(\mathrm{ml/min/1.73m^2}\right)=141\times\min\left(\frac{SCr}{\kappa},1\right)^{\alpha}\times\max\left(\frac{SCr}{\kappa},1\right)^{-1.209}\times 0.993^{\mathrm{Age}}\times 1.018\left[\mathrm{if\ female}\right]\times 1.159\left[\mathrm{if\ African\ American}\right]$$

Where:
SCr is serum creatinine in μmol/L,
κ is 61.9 for females and 79.6 for males,
α is −0.329 for females and − 0.411 for males,
min indicates the minimum of SCr/κ or 1, and
max indicates the maximum of SCr/κ or 1

$$\mathrm{CKD-EPI} \tag{24.3}$$

Both of the above equations are normalized to 1.73m^2 body surface area. Online calculators are readily available for clinicians to utilize these formulas. As with the Cockcroft-Gault formula, they should only be used with stable chronic kidney disease, not in patients with acute kidney injury.

Blood Urea Nitrogen (BUN) (Reference Range 2.9–8.2 mmol/L)

BUN is the concentration of nitrogen (as urea) in the serum. Its serum concentration depends on urea production which occurs in the liver, GFR, and tubular reabsorption. On its own, it cannot be used to predictably assess renal function. In conjunction with other laboratory data, it can be used to monitor hydration, renal function, and protein tolerance and catabolism. It can also be used to predict the risk of uremic syndrome in patients with severe renal failure. An elevated BUN can occur with high protein diets, upper GI bleeding, dehydration and/or volume depletion, or acute kidney injury. Usually, a low BUN does not have physiological consequences, but may be low in

the presence of malnutrition or individuals who have extensive liver damage.

Urine Protein (Proteinuria)

Healthy individuals normally excrete very small amounts of smaller molecular weight proteins in the urine (10–150 mg/day). In the presence of kidney damage, the glomerulus becomes more permeable to larger proteins including albumin. Increased albumin excretion (albuminuria) can occur in the setting of diabetic nephropathy, glomerular disease, and hypertension. Table 24.3 describes the relationship of albuminuria and proteinuria to severity of renal dysfunction.

Other Urinalyses

Urinalysis to look for blood cells, cellular casts, specific gravity, and sodium may provide additional information as to presence of kidney injury. Table 24.4 summarizes the various urinalysis tests relevant to assessing kidney function.

Hematuria refers to the presence of red blood cells (RBC) in the urine. A few RBC may normally be seen in the urine under microscopy. Red blood cells of >3/high-powered field may be indicative of intrinsic renal failure, infection, or a consequence of damage from renal stones or trauma. Women of child-bearing age may have some residual RBCs in the urine as a result of menstruation.

Pyuria refers to the presence of white blood cells (WBC) or leukocytes in the urine. Again, it may be normal to find a few white blood cells under microscopy. Large amounts of WBCs may indicate the presence of inflammation or infection in the urinary tract. They may also be seen in interstitial nephritis.

Table 24.3 Albuminuria/proteinuria and severity of renal impairment [9]

Measure	Normal-mild	Moderate	Severe
Albumin excretion rate (mg/24 hours)	<30	30–300	>300
Protein excretion rate (mg/24 hours)	<150	150–500	>500
Albumin/creatinine ratio (mg/mmol)	<3	3–30	>30
Protein/creatinine ratio (mg/mmol)	<15	15–50	>50
Urine dipstick	Negative to trace	Trace to +	+ or greater

Table 24.4 Urinalysis tests

Parameter	Reference range/normal findings	Comments
Red blood cells	1–3/high-powered field (HPF)	Persistent hematuria may be seen in glomerulonephritis, infection, renal stones
White blood cells	0–2/HPF	May be present in conditions such as interstitial nephritis
Specific gravity	1.016–1.022	Correlates with kidneys' concentrating ability and will be increased or decreased depending on various physiological or disease processes
Urine sodium	Variable	Often used to assess volume status and acute kidney injury
$\%FE_{Na}$	Variable	Used in assessing acute kidney injury

$\%FE_{Na}$ the fractional excretion of sodium

Casts are cylindrical masses of glycoproteins formed in the renal tubules. There are different types of casts depending on the types of cells they form around. For example, red cell casts form around RBCs, white cell casts around WBCs, or epithelial cell casts. There are also clear or hyaline casts, which are usually not an indication of a specific disease process. The presence of WBC casts typically indicates infection or inflammation, and RBC casts and epithelial cell casts usually are representative of significant damage to the kidney.

Specific gravity is an indication of the kidneys' ability to concentrate urine. Specific gravity (SG) is the ratio of the weight of a given fluid to the weight of an equal volume of distilled water. Patients with normal kidney function and normal fluid intake have a SG between approximately 1.016 and 1.022, but can dilute urine to approximately 1.001 and concentrate urine to approximately 1.035. A specific gravity of 1.010 indicates that the urinary osmolality is the same as the plasma (isosthenuric). Individuals who are volume-depleted, such as in prerenal failure, would present with a concentrated urine (SG ≥1.022), whereas patients with intrinsic

renal failure would have kidneys that would be unable to dilute or concentrate urine, so SG would remain around 1.010.

Urinary sodium concentration and $\%FE_{Na}$ are helpful indicators of a patient's volume status and can vary depending on clinical status and presence of kidney damage or other disease processes. The $\%FE_{Na}$ is the fraction of sodium that is filtered by the glomerulus eventually excreted in the urine and is useful in distinguishing types of acute kidney injury.

Types of Kidney Dysfunction

Acute Kidney Injury

Acute kidney injury is defined by an abrupt decrease in kidney function that includes but is not limited to acute renal failure. A patient is experiencing AKI when any of the following criteria are met [10]:

- Increase in serum creatinine by ≥26.5 μmol/L within 48 hours; or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine output <0.5 ml/kg/h for 6 hours

The staging of AKI can be assessed based on serum creatinine and urine output criteria as outlined in Table 24.5 [10].

Table 24.5 Staging of acute kidney injury (AKI) [10]

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline *or* ≥26.5 μmol/L increase	< 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline *or* Increase in serum creatinine to ≥353.6 μmol/L *or* Initiation of renal replacement therapy *or*, in patients <18 years, decrease in eGFR to <35 ml/min/1.73 m^2	<0.3 ml/kg/h for ≥24 hours *or* Anuria for ≥12 hours

Patient Assessment

It is important to be able to identify patients who may be at risk of developing AKI. These include patients receiving potentially nephrotoxic drugs, the elderly, or who may be experiencing or at risk of the following conditions:

Volume depletion (severe burns, blood loss, dehydration)	Renal artery stenosis
Cirrhosis with ascites	Renal artery or vein thrombosis
Heart failure	Glomerulonephritis
Cardiomyopathy	Benign prostatic hypertrophy
Hypotension/shock	Nephrolithiasis
	Chronic kidney disease

Patients at risk of AKI should have a baseline serum creatinine measured when their kidney function is stable, to assess for changes over time to determine if there is an acute deterioration in renal function. When no baseline value is available, often repeat serum creatinine measurements can be used to assess the rate of deterioration or urine output can be measured. This information, along with the clinical history of the patient, can be used to determine if the individual meets the criteria for AKI.

Symptoms

Signs and symptoms of acute kidney injury may be nonspecific but can include changes in urinary habits, sudden weight gain, or flank pain. Other signs may include edema, orthostatic hypotension, colored or foamy urine, or hypertension.

Classification of AKI

AKI can be divided into three categories based on their different etiology, pathophysiology, and management: prerenal, intrinsic, and postrenal [11].

- *Prerenal injury* is a functional response to renal hypoperfusion and is not associated with a structural injury to the kidney itself.
- *Postrenal* AKI results from obstruction of the urinary collecting system. Obstruction may occur at the level of the bladder, urethra, ureters or renal pelvis. This must occur in both kidneys in order to cause AKI.

Table 24.6 Causes of acute kidney injury

Prerenal	Postrenal	Intrinsic
Hypovolemia	Nephrolithiasis	Ischemic causes
Hemorrhage	Blood clots	Hypotension
Cutaneous losses (burns, sweat)	Surgical injury	Hypovolemic shock
Gastrointestinal losses (diarrhea, vomiting)	Malignancy	Sepsis
Renal losses (diuresis)	Neurogenic bladder	Systemic lupus erythematosus
Decreased effective blood volume	Prostate cancer	Hemolytic-uremic syndrome
Heart failure	Benign prostatic hypertrophy	Renal artery thromboembolism
Cirrhosis	Urethral strictures	Multiple myeloma
Nephrotic syndrome	Drug-induced	Ethylene glycol ingestion
Intrarenal vasoconstriction		Drug-induced
Hepatorenal syndrome		
Drug-induced		

Table 24.7 Differentiating type of AKI based on laboratory findings

	Acute kidney injury type		
Laboratory tests	Prerenal	Intrinsic	Postrenal
Urine sediment	Normal	Casts, cellular debris	Cellular debris
Specific gravity	↑	↓ or ↔	↔
Urinary RBC	None	2–4+	Variable
Urinary WBC	None	2–4+	1+
Urine sodium (mmol/L)	<20	>40	>40
FE_{Na}(%)	<1	>2	Variable
BUN	↑↑	↑	↑
Serum creatinine	↑↑	↑↑	↑↑

%FE_{Na} the fractional excretion of sodium, *BUN* blood urea nitrogen, *RBC* red blood cells, *WBC* white blood cells

- *Intrinsic* AKI occurs due to an injury to a structural component of the kidney. There are four main types of intrinsic AKI based on the location of the injury: tubules, interstitium, glomerulus, vascular capillaries.

Causes of each type of AKI are outlined in Table 24.6 [11]. Various laboratory parameters can be used to help confirm the type of AKI the patient is experiencing in conjunction with additional clinical information. The relevant laboratory parameters are summarized in Table 24.7.

Ongoing Assessment and Monitoring

Treatment goals of AKI include minimizing the degree of insult to the kidney, reducing extrarenal complications, and expediting the patients' recovery of renal function. General treatment includes hydration, discontinuing any nephrotoxic agents, and treatment of underlying conditions contributing to the injury. Diuretics, in particular loop diuretics like furosemide, are used if there is volume overload. Renal replacement therapy (dialysis) is used when correction of electrolyte imbalances is required, particularly with increased potassium, fluid overload, and when removal of uremic or other toxins is necessary.

Individuals should have daily or more frequent monitoring of their serum creatinine and urinary output to help assess recovery of renal function. Additional monitoring should include electrolytes, BUN, fluid status, and blood pressure. If kidney function recovers, patients should receive regular monitoring of their kidney function as they are at an increased risk of developing chronic kidney disease throughout their lifetime.

Chronic Kidney Disease

Chronic kidney disease (CKD) is a progressive loss of kidney function over a period of months or years. More specifically, it can be defined as either kidney damage or a glomerular filtration rate (GFR) of <60 ml/min/1.73m^2 for ≥3 months [9]. Classification of CKD is provided in Table 24.8.

Patient Assessment

Screening for CKD should be targeted for individuals at increased risk of developing CKD including the following [12]:

Table 24.8 Classification of chronic kidney disease [9]

Stage	Description	GFR(ml/min/1.73m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure/end-stage renal disease	<15 or dialysis

GFR glomerular filtration rate

Table 24.9 Nephrotoxic drugs

Angiotensin receptor blockers Angiotensin converting enzyme inhibitors Antineoplastics (mitomycin, cisplatin, methotrexate) Antimicrobials (aminoglycosides, amphotericin B, vancomycin, cephalosporins, penicillins, sulfonamides)	Antivirals (acyclovir, indinavir, tenofovir) Radiographic contrast dyes Diuretics Lithium Nonsteroidal anti-inflammatory drugs (NSAIDs)

- Hypertension
- Diabetes mellitus
- Family history of stage 5 CKD
- Hereditary kidney disease
- Previous history of acute kidney injury
- Vascular disease
- Multisystem disease with potential kidney involvement (e.g., systemic lupus erythematosus)
- Advanced age

Individuals should also be assessed for current or prior use of nephrotoxic drugs, which may cause AKI or contribute to progression of CKD (Table 24.9).

Screening for CKD should include a serum creatinine (and associated eGFR), a random urine albumin or protein/creatinine ratio, and urinalysis. An eGFR of <60 ml/min/1.73m^2 for ≥3 months is diagnostic for CKD. A new finding of a reduced eGFR should prompt repeat testing to exclude causes of acute deterioration of eGFR such as acute kidney injury.

Symptoms

At early stages of CKD, patients are largely asymptomatic. In stages 3–5 CKD, patients may begin to experience general symptoms related to fatigue, edema, and decreased urine output. Cardiovascular symptoms may arise related to hypertension, heart failure, pericarditis, and atherosclerosis. With the accumulation of uremic toxins, individuals may experience nausea and vomiting, anorexia, bleeding, and pruritus. Neuromuscular symptoms include restless leg syndrome, muscle cramps, impaired cognition, and peripheral neuropathy. Anemia may also be present at the later stages of CKD due to the kidney's inability to produce erythropoietin. An imbalance of calcium and phosphate homeostasis and vitamin D metabolism may contribute to signs and symptoms related to renal bone disease such as bone pain and increased risk of fractures.

Ongoing Assessment and Monitoring of Patients with CKD

Individuals with CKD are usually initiated on therapy to slow progression of renal impairment with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). Within 2 weeks of initiation or dosage increases, patients should have their potassium and eGFR checked. ACEi and ARBs can cause a reversible reduction in eGFR when beginning therapy. General recommendations for assessment and management include [12]:

- Start at lowest dose of ACEi or ARB and titrate up slowly to maximum tolerated dose
- Stop ACEi or ARB if the reduction in eGFR exceeds 25% from baseline
- Recheck eGFR in 2–3 weeks if reduction in eGFR is 5–25% from baseline
- Increases in serum potassium can be expected of up to 0.5 mmol/L

Certain medications that are renally excreted or may potentially be nephrotoxic should be temporarily held in the setting of acute illnesses where patients are unable to maintain adequate fluid intake until they have recovered. In this clinical setting, continuing these medications may increase the risk of the patient experiencing acute kidney injury or adverse effects. The medications include sulfonylureas, ACEi/ARB, diuretics, metformin, and NSAIDs [12].

Individuals with CKD are also at increased risk for cardiac disease and should be assessed to ensure they are receiving appropriate therapy to reduce their overall cardiovascular risk. This includes assessing patients for initiation of statin and antiplatelet therapy. Statin therapy is generally recommended for all patients with CKD and diabetes unless there are contraindications [13]. In patients without diabetes, patients aged >50 years should receive a statin and those <50 years should receive statin therapy if they have known cardiovascular disease or prior ischemic stroke, or if their estimated 10-year incidence of cardiovascular disease is >10% [14]. Low-dose aspirin therapy can be used for secondary prevention in patients with established cardiovascular disease where there are no contraindications [15].

Finally, all patients with CKD should have regular assessments of their drug therapy to determine if dosage adjustments are required. This should occur at regular intervals whenever the patient has a new eGFR calculated or a new medication is initiated, including nonprescription therapies. A general approach to adjusting drug dosages is outlined as follows [16]:

- Obtain patient history including relevant demographic and clinical history.
- Calculate creatinine clearance using an appropriate weight-adjusted or nonweight-based formula, compared to eGFR from lab results.
- Review current medications and determine which drugs may require dosage adjustment.
- Consult one or more drug-dosing references to determine an appropriate dosage.
- Monitor for response to drug as well as for adverse effects.
- Revise regimen if required based on response and clinical status.

Clinical Pearls

- Pharmacists have an important role in the assessment and monitoring of both acute kidney injury and chronic kidney disease.
- A systematic assessment process includes evaluation of relevant markers of kidney function in conjunction with the patients' clinical history and presentation.
- Targeted screening and assessment of kidney function should occur in those patients at highest risk, including those with diabetes, hypertension, vascular disease, the elderly, and those receiving renally eliminated or potentially nephrotoxic drugs.

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Infectious Disease Assessment

25

Cecilia Lau

Chapter Objectives

1. Describe the core elements of approach to infectious disease assessment.
2. Describe the use of empiric, definitive, and prophylactic antimicrobial therapies.
3. Describe the use of an antibiogram.
4. Describe the approach to interpretation of culture results.

Background

Infectious diseases encompass illnesses associated with infection from pathogenic bacteria, fungi, protozoa, and viruses. The epidemiology and incidence of specific disease varies depending on extrinsic and intrinsic factors to the host. History and physical exam for signs and symptoms will often suggest a probable diagnosis. In selected patients, this diagnosis can be confirmed by obtaining specimens for culture, serology, polymerase chain reaction identification, microscopy, and pathology when indicated. Imaging and procedures may further assist with the diagnosis. Microbiological surveillance of common isolates in specific illnesses has allowed clinicians to identify the most common organisms associated with specific infections. This has also allowed accumulation of susceptibility patterns, presented in antibiograms. Additional consideration must also be given regarding host exposures to likely pathogens in the age of global travel when antimicrobial resistance pattern can differ. Globally, infectious syndromes may have similar pathogenesis, diagnostic workup, and common pathogens, allowing empiric treatment. However, the prescribed antimicrobials should be tailored to the identified pathogen, its susceptibility, pharmacokinetic/pharmacodynamics parameters, availability of an antimicrobial and patient tolerability. Judicious prescribing of antimicrobials at every opportunity is required to decrease unnecessary use of broad-spectrum antimicrobials, which is associated with increased cost, resistance, and exposure of patient to adverse effects. The ultimate goal is to prolong the longevity of all antimicrobials in the era of increased global antimicrobial resistance.

In clinical practice, pharmacists are tasked to maintain competency in the management of different infectious syndromes, acquire knowledge on novel antimicrobials, and minimize the impact of inappropriate use of antimicrobials while ensuring resolution of an infection. Pharmacist intervention encourages adherence to guideline directed care in infectious disease with specific tailoring to ensure antimicrobial indication, dosing regimen, choice based on site of infection and duration of treatment

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are appropriate. As medication stewards, the role of the pharmacists has been specifically highlighted as champions for implementation of Antimicrobial Stewardship Program (ASP). Pharmacists working in all practice settings have an important role in ASP as they possess the unique skills and expertise to provide tailored advice based on disease and patient factors.

Approach to Infections with "I.N.F.E.C.T.I.O.N.S."

The collaborative approach to infections can be divided into core elements. Key pharmacists' roles for each of the elements or highest impact interventions are as listed in Table 25.1, which may vary depending on the practice setting.

Infection and/or Indication for Each Antimicrobial Prescribed Must Exist

Humans live in harmony with a plethora of microorganisms, some of which possess the capacity to cause disease. Microbial flora may be classified as residential flora, which are found consistently at a site and promptly reestablish their presence if disturbed, or transient flora, which may colonize the host for a specific time period but do not permanently establish themselves. Furthermore, microorganisms colonize different parts of the body based on tissue tropism as well as the presence of an ideal habitat. Thus, the normal organisms that live on the skin are appreciably different than what live in different parts of our gastrointestinal tract based on factors such as oxygen, natural host defense with gastric acid, etc. When host defenses are

Table 25.1 Approach to infections

	Core Element	Pharmacist Role
I	Infection and/or indication for each antimicrobial prescribed must exist.	Recognize if an infection or indications for each antimicrobial exist. Intervene when an antimicrobial is not indicated. Intervene when there is therapeutic duplication. Intervene when additional antimicrobial is required.
N	Not working alone in making therapeutic decisions.	Collaboration with other healthcare team members. Pharmacists are the medication experts and are frequently consulted to ensure optimal dosing regimen (drug, dose, route, duration) are prescribed for the indication and the sites involved.
F	Foci of infection should be assessed for source control, impact on choice, and duration of therapy.	Anticipate impact of presence or absence of source control on duration of therapy.
E	Empiric therapy should target common pathogenic organisms with consideration of additional risk factors.	Intervene when empiric therapy is inappropriate for suspected infection.
C	Culture to be done in clinically relevant specimens in selected patients.	Interpret preliminary and final culture and sensitivity result and recommend modifications to empiric or definitive therapy.
T	Timing of first antimicrobial exposure has implications.	Intervene when delay in prescribing is appropriate. Intervene when therapy should not be delayed.
I	Inquire into allergies, organ functions, genetic/metabolic abnormalities.	Determine the appropriate drug choice and dosing regimen tailored to patient.
O	Ongoing assessment and monitoring required.	Determine if dose and interval of empiric therapy is appropriate based on indication and organ function.
N	Narrowest-spectrum antimicrobial should be used whenever possible and applicable.	Determine if streamlining to narrowest-spectrum antimicrobial is appropriate. Intervene as necessary.
S	Seamless care	Pharmacists play an important role in counseling on the medications prescribed and to assess efficacy, tolerability, and ensure compliance. Pharmacists can maximize the future care of these patients by clear documentation of a patient's intolerance to an antimicrobial.

breached, some organisms that normally live in symbiosis with the host may cause disease. Acquisition of a pathogenic organism is also possible from exposure to communicable pathogens under the right circumstances (e.g., viruses responsible for Ebola, influenza). Some infections will also require additional vectors for transmission to occur such as the deposit of *Plasmodium* sporozoites into an individual while an infected *Anopheles* mosquito is taking a blood meal, transmitting malaria that is endemic in certain parts of the world, limited by the natural habitat of the mosquito. Thus, causative pathogens of infectious diseases may be intrinsic to the host or extrinsically acquired.

Signs and Symptoms Suggestive of Infections

With the milieu of organisms living within us as well as continuous exposure to the outside world, familiarity with common signs and symptoms associated with infection will alert clinicians to the possibility of infection. General warning signs can include fever and chills, hypothermia, tachycardia, tachypnea, nausea, vomiting, diarrhea, decreased appetite, decreased urine output, or abnormal mentation. Some infections may have pathognomonic findings but in general the differential diagnosis can be wide and varied when most patients present with such nonspecific signs and symptoms. Different infections can have different signs and symptoms as they originate from different parts of the body and also largely reflect an individual's response. Specific localizing signs may be present on exam such as swelling or erythema surrounding an infected joint or costovertebral pain in pyelonephritis. An examination of bloodwork, when available, may reveal abnormalities in white blood cell counts or a rise in inflammatory markers. Yet, none of these signs and symptoms is specific to infections only as many noninfectious causes exist for the same presentation. To illustrate, a patient with severe medication allergy may present with generalized rash, high fever, leukocytosis driven by eosinophilia with high inflammatory marker and does not signify that an infection exists; this is the body's adverse reaction to a medication. In addition, signs and symptoms are particularly difficult to interpret and may be absent at the extremes of the age spectrum or in immunocompromised patients.

Antimicrobial Indication Broadly Defined

Regardless whether an infection is present or not, there should be a clear indication for each antimicrobial prescribed as outlined in Fig. 25.1. Antimicrobials are utilized to prevent or treat infections. Thus, patients prescribed antimicrobial may or may not have an infection. Prophylaxis is used to prevent infections when patient, procedural, or situational-specific factors increase the risk for certain infections. These patients do not have an existing infection but are considered at risk. Treatment is categorized into empiric and definitive therapy. These patients have a suspected or documented infection and require effective therapy.

Primary prophylactic therapy is prescribed to prevent a first infection (e.g., surgical prophylaxis, posttransplant opportunistic infection, AIDS patients with low CD4 counts). The choice and duration of the required preventive therapy varies depending on each situation, duration of perceived risk and pathogens targeted. Surgical prophylaxis is of finite duration, usually $\leq$24 h postoperatively, whereas some posttransplant prophylaxis is continued lifelong. *Secondary prophylaxis* is prescribed to prevent the recurrence of a previously documented infection after a treatment course has been completed. Evidence-based guidelines exist for many of the aforementioned at-risk patient populations and should be adhered to.

Empiric therapy is defined as the use of antimicrobial to provide coverage of the most likely pathogens in specific infections or based on likelihood of effectiveness when a pathogen is identified but the result of the isolate's susceptibility is unknown at the time of prescribing. Although presumptions can be made based on known spectrum of activity of the different classes of antibiotics, other factors such as local resistance pattern will often define which antimicrobials are the preferred choices within a geographical

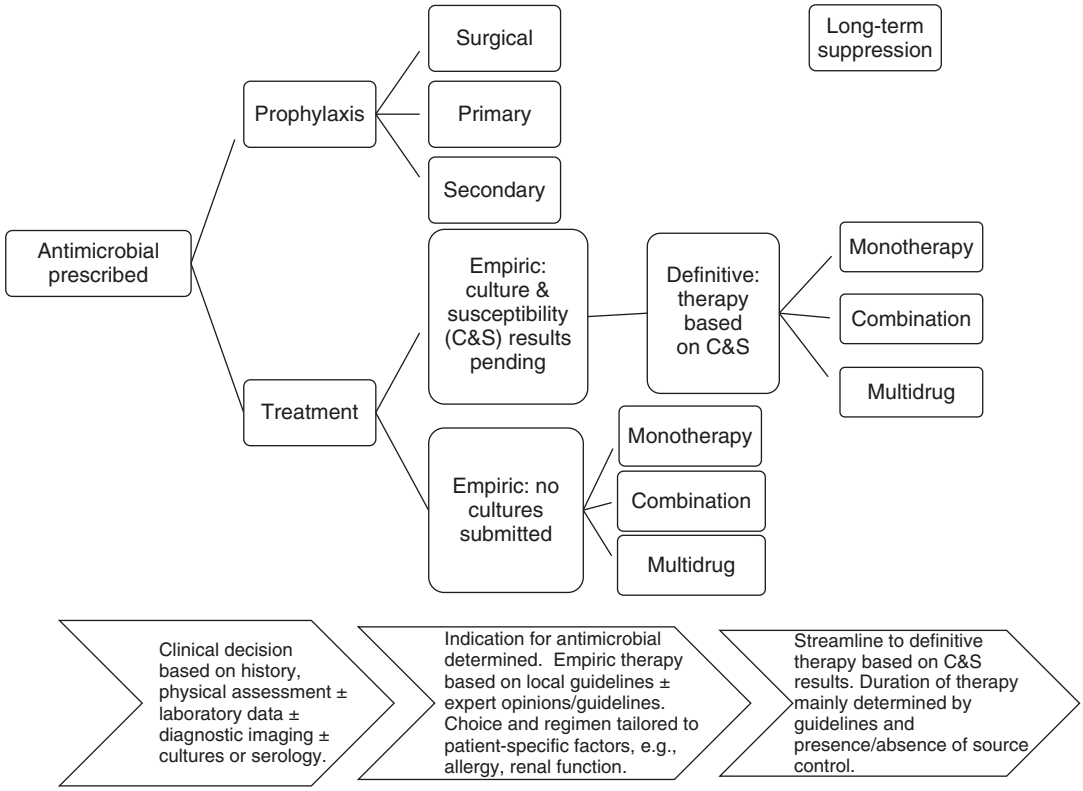


Fig. 25.1 Indications for the prescribed antimicrobial therapy. C&S culture and sensitivities

location. Even within an institute, the susceptibility patterns can vary greatly amongst different wards and changes over time based on patterns of antimicrobial usage.

Definitive therapy, also known as targeted therapy, is based on susceptibility data. The antimicrobial prescribed may be narrower or broader in its spectrum of activity than the empiric therapy. Whenever possible, the narrowest agents are preferred to minimize overall antibiotic exposure that can have downstream effect on resistance profiles. When narrower spectrum antimicrobial is chosen, the perceived benefit of streamlining includes improvement in resistance profile, decreased adverse events, decreased length of stay in hospital, and cost savings to patient and healthcare [1]. Hesitancy to modify a chosen regimen includes complex susceptibility pattern in a polymicrobial infection, inability to discern contamination or colonization from pathogenic existence of the identified organisms, concerns regarding the reliability of antimicrobial influenced culture results, and the perception that the patient is improving with empiric, often broader-spectrum, antimicrobial therapy.

Lifelong suppression therapy is an ill-defined hybrid of secondary prophylaxis and definitive therapy. Although an appropriate treatment course of an infection has been completed and no evidence-based guideline exists to support the continuation of treatment, some infections may be deemed incurable and the attending specialists may choose to prescribe prolonged suppression therapy. Paucity of data makes determining the right dosing regimen difficult where one prescriber may choose a lower dose, while another may choose a higher dose, with both based on experience. In one study on prolonged antibiotic use defined as 1 year and longer, 43/202 (21%) were prescribed long-term suppressive antimicrobial therapy for infected prosthetic devices (valves, cardiac devices, arthroplasty, spinal

fixation), chronic osteomyelitis (OM), and vascular graft infections; 34/43 (79%) were prescribed by infectious disease specialists [2]. This highlights the importance of transparency in prescribing especially regarding specific unique decisions made after careful deliberations between the patient and the prescriber.

Not Working Alone in Making Therapeutic Decisions

In patient care, clinical assessment, diagnostic investigations, and therapeutic decisions often occur as a continuous and overlapping process that involves many team members. Signs and symptoms elucidated by a clinician's history and physical exam will often identify a wide range of differential diagnosis that may include infections. Clinicians should be cognizant of specific host-related factors that influence the likelihood of contracting an infection such as a patient's overall immune status from acquired or congenital disease or iatrogenic immunodeficiency from splenectomy or immunosuppressive therapy. In susceptible individuals, exposure to animals (e.g., playful bites from a cat, affectionate licking of open wounds by a dog) can cause diseases ranging from cellulitis, bacteremia, to osteomyelitis. Sick contacts are also important to note as general knowledge of transmission, incubation, and timeline to disease manifestations helps narrow down potential infectious etiology. For the same reason, recent or remote travel history for work, leisure or missionary trips may reveal a risk of acquiring endemic infections specific to the geographic location. Altogether, a collaborative patient intake assessment can offer insight to foci of an infection, probable causative pathogens, and evaluation of actual or potential complications from the infection.

Currently, pharmacists' training does not include in-depth history taking, physical exam, and interpretation of many diagnostic investigations, all of which are crucial to the management of various infectious diseases. Interdisciplinary collaboration is encouraged whenever possible as individual team members contribute their expertise to improve the quality of patient care. As a team, every patient should be assessed for severity of illness, potential source of infection, need for diagnostic investigations while contemplating the choice of empiric antimicrobial therapy and the necessity of other pharmacologic and non-pharmacologic interventions. Common indications for additional tests ordered include:

1. To diagnose or support the diagnosis
2. To identify the foci of an infection and assess for possible complications
3. To decide if further culture for isolation of culpable organism(s) is possible or required
4. To determine if an infection is amenable to source control

Thus, patient care process in infectious diseases may often involve team members due to their specialist knowledge pertaining to their area.

Pharmacists are, however, the medication experts and are frequently consulted to ensure optimal dosing regimen (drug, dose, route, duration) are prescribed for the indication and the sites involved. The choice of the antimicrobial may be impacted by the distribution characteristic of an agent. For example, in meningitis, the chosen antimicrobials must have adequate blood–brain barrier penetration and also ideally be bactericidal as central nervous system lacks many of the natural host defense mechanisms. In addition, dosing can be complex as individual antimicrobial may be impacted by organ function relevant to its clearance. Continuous assessment is required to ensure appropriate adjustments are made based on worsening or normalization of organ functions. Finally, antimicrobials can certainly have drug–drug or drug–disease interactions or contraindications such as the substantial decrease of valproic acid levels in patients treated with carbapenems or exacerbation of myasthenia gravis from aminoglycoside use. For these reasons, antimicrobial therapy guidance from pharmacists plays an important role. In turn, pharmacists may rely on team members (most responsible physician, interventional radiologist, general surgeon, nurse clinician, physician assistant) to confirm that improvement has been documented.

Foci of Infection Should Be Assessed for Source Control, Impact on Choice and Duration of Therapy

Source Control

Strategies to remove the foci of infection are known as source control. It may involve minimally invasive procedures or invasive operations for the purpose of drainage, debridement, or resection. The decision of whether source control is needed or should be attempted depends on many factors and often requires assessments from various specialists. It may also depend on the severity of illness. For example, a patient with acute abdomen in septic shock found to have perforated viscus on imaging will benefit from immediate life-saving surgical intervention involving washout of fecal peritonitis, control of perforation with immediate or delayed of reestablishment of gut continuity. On the other hand, a clinically stable patient found to have contained ruptured appendix may be conservatively treated for days with antimicrobial while awaiting surgery. For catheter-associated bloodstream infections (CABSI), the removal of the infected line and insertion into a different site when the continued need for intravenous access exists increases the success of medical therapy and significantly decreases the chance of recurrence, especially for the virulent and biofilm-loving pathogens such as *Staphylococcus aureus*. In contrast, when some less virulent coagulase-negative *Staphylococcus* species are isolated in CABSI, a reasonable approach is to retain the line and treat with antimicrobials in patients with difficult vascular access. Furthermore, situations may exist where the risks of a procedure outweigh the benefits of source control (e.g., multiple redo open-heart valve replacements subjecting patient to surgery-related risks of complications, including renal failure, ischemic bowel, sternal wound infections, heart block, etc.).

Impact on Choice of Therapy

For an antimicrobial to achieve a therapeutic effect, an adequate amount of the drug must be delivered to the site of infection. The ability to achieve or detect local concentrations at the site of infection is desirable, but its consequence is not certain. Generally, the local concentration of the antimicrobial should be at least equivalent to the minimum inhibitory concentration of the targeted organism, although it has been suggested that higher multiples may be more efficacious. There is evidence to suggest that even at subinhibitory concentrations, the antimicrobial may still exert positive influences on the host defenses against infections through altering bacterial morphology, adherence properties, enhanced phagocytosis, and promote intracellular killing of bacteria by leukocytes [3]. Clinical cure may still be possible with lower than desired concentration at the site of infection, but the approach to patient care should target utilizing therapy with the highest probability of optimal outcome.

Antimicrobial choice and dosing should be appropriate for the targeted site of infection. In addition to being proven effective for a given pathogen in an in vitro setting, antimicrobial prescribing must consider each agent's ability to reach the site of infection, dosing modification required to achieve effective concentration, and, all else being equal, final selection may be based on the perceived benefit of the pharmacodynamics parameters associated with the antimicrobial. Experience and bodies of literature continue to accumulate regarding known difficult-to-penetrate sites of infection such as in the central nervous system, ophthalmic, bone, and prostate infections, which are reflected in many point-of-care references. Some examples where the site of infection is important to the choice and dose of antimicrobial prescribed include daptomycin use in lung infections, tigecycline use in bacteremias, and the choice of antimicrobials based on the foci of postneurosurgery infections. Daptomycin, although a reasonable alternative for susceptible gram-positive infections, cannot be recommended in pneumonia as the drug is inhibited by the pulmonary surfactant, a primary component of the epithelial lung fluid lining the lung surfaces. Proposed mechanism of inhibition includes insertion of daptomycin into the lipid aggregates of the surfactant, thus sequestering and inhibiting the action of the antibiotic. Tigecycline has excellent distribution in the body but its resultant low serum concentration has been associated with breakthrough recurrence in the off-label treatment for bacteremia with susceptible pathogens. First-generation cephalosporins (e.g., cefazolin) are

effective for most surgical site infections and are routinely recommended in guidelines. However, if the surgical infection involves a deep organ space where penetration of antimicrobials is known to be problematic, the choice changes to include coverage with antimicrobials that offers proven penetration to the site of infection. In post-neurosurgery with image-proven brain abscesses or ventriculitis, for maximal penetration and potential pathogen coverage, antimicrobials prescribed at the highest dose appropriate to the patient's organ function may be meropenem 2 g IV every 8 h plus vancomycin IV dosed to target steady-state trough of 15–20 mg/L. Conversely, if the post-neurosurgery surgical infection is limited to a superficial wound infection, cefazolin or other alternatives, including oral agents, may be appropriate.

Impact on Duration of Therapy

Pharmacists play an instrumental role in assessment of many aspects of prescribing including appropriate duration of therapy. Table 25.2 provides examples of duration of therapy recommended currently for common infectious syndromes where anatomical sites, source control and other factors may impact the duration of therapy. As evidence continues to accumulate, clinicians may see duration lengthened or shortened for various infections in guidelines and point-of-care references. In addition to source control, duration of therapy may be influenced by the site of infection, immune status of the patient, and the causative pathogen. Further tailoring is recommended based on patient response to therapy in specific infections. Pharmacists are unlikely to participate in source control but our assessment of a patient should include inquiry into the feasibility of source control to anticipate its impact on antimicrobial treatment.

One must, however, be mindful that not all infections require source control such as for uncomplicated urinary tract infections, pneumonia, or meningitis. The same indications with complicated circumstances may necessitate the removal of a long-standing indwelling Foley catheter, debridement of an empyema, or replacement of a ventriculoperitoneal shunt. In selected infections, if source control is incomplete or cannot be performed, a longer-than-usual duration may or may not be required. If the nidus of an infection has been removed and there is no concern for residual infection,

Table 25.2 Examples of duration of antimicrobial therapy impacted by foci of infection, source control, and other factors

Site	Infections	Duration of Therapy	Impact of Foci Identification and Source Control
Bacteremia	Foci removed	10–14 days	From clearance of bacteremia or removal of foci.
Bone	Osteomyelitis	Acute → 42 days Chronic → treat till ESR normalizes, may be ≥90 days	Dependent on the causative pathogens and acuity of the infection. If source removed with amputation distal to the site of infection, and no other foci of infection identified, may stop treatment ≤2 days post-op.
Heart	Endocarditis – native valve	*Staphylococcus aureus* Mitral/aortic valve, uncomplicated → 28–42 days Tricuspid valve, uncomplicated → 14 days *Streptococcus viridans* → 14–28 *Enterococcus* species → 28–42	Dependent on the causative pathogens, patient specific factors, as well as valve(s) involved. Duration of a regimen chosen for a specific organism may be impacted by a pathogen's MIC and the patient's ability to tolerate the chosen therapy. Due to anatomy of the valve and small area for debridement, and lack of data, short-course postoperative antibiotic cannot be suggested. A full course of treatment based on causative pathogen is required. In general, if the removed valve sent for culture demonstrates no growth, treatment may start from documented clearance of bacteremia, whichever is sooner.
Joint	Septic arthritis	14–28 days	Arthroscopic or open debridement of joints is desirable to minimize damage to joint from cytokines-induced inflammatory reaction.

ESR erythrocyte sedimentation rate

antimicrobial therapy may be appropriately discontinued despite indication-specific guideline recommended duration of treatment. Suppose a patient diagnosed with image-proven left foot osteomyelitis (OM) that evolved from chronic bilateral diabetic foot ulcer undergoes a left below-knee amputation, therapy for the left foot OM should be shortened from ≥6 weeks to ≤48 h postoperatively to decrease stump infection rate. However, the right foot remains and, when assessed clinically, requires appropriate wound care in addition to a short course of antimicrobial therapy. If this same patient presented with bacteremia, but workup is negative for disseminated or metastatic disease, the most appropriate therapy would be an antimicrobial that will effectively treat both the bacteremia and the diabetic foot ulcer with duration determined by whichever indication requires the longer course.

Empiric Therapy Should Target Common Pathogenic Organisms with Consideration of Additional Risk Factors

Some common medically important bacteria are presented in Fig. 25.2 based on Gram stain cell wall morphology. Preliminary growth and Gram stain identification is labor-intensive. It requires interpretation and further biochemical tests to confirm the identification. Similarly, identification of viral, fungal, and protozoan pathogens

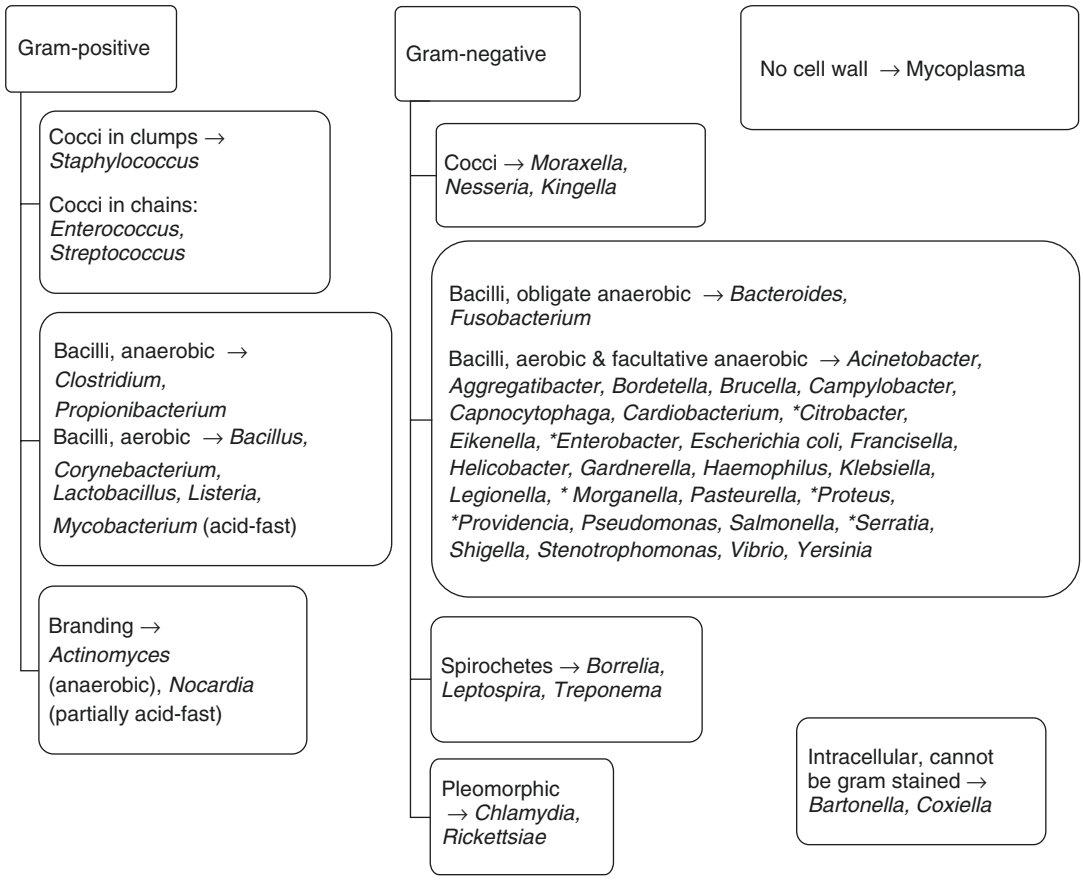


Fig. 25.2 Common potentially medically important bacteria classified based on Gram stain morphology of the cell wall. *Inducible AmpC beta-lactamase producers SPICEM (*Serratia, Providencia, Indole positive Proteus* = *Proteus vulgaris, Citrobacter, Enterobacter, Morganella*)

must also follow specific protocols to identify the organism. Some organisms do not grow well in artificial media. Thus, other techniques such as nucleic acid testing, serology, and microscopy must be employed where applicable and available. Each organism is capable of causing a range of infections unique to it that are often present as one manifestation, although concurrent manifestations in the same patient may be possible. Until more rapid and reliable testing is widely available, clinicians must continue to rely on existing knowledge on these pathogens and the specific infectious syndromes attributable to them.

Fortunately, widely available references exist to offer guidance to clinicians when initiating empiric therapy based on a suspected diagnosis. A list of references commonly used by practitioners involved in care of patients with infection is provided in Table 25.3. Adherence to local guideline whenever possible can maximize the likelihood of prescribing the most appropriate therapy based on local susceptibility pattern of the suspected pathogens, availability of antimicrobials, and cost to patient and healthcare system. Where no reference exists, or may be incomplete, pharmacists can assist their team to make the best decisions by participating in evidence-based medicine review of available primary literature. Based on the suspected infectious diagnosis, patients should be prescribed an antimicrobial with dosing regimen tailored to host factors.

Table 25.3 Commonly used references in infectious disease patient care

Reference	Comments	Cost
Antimicrobial and treatment-focused bedside references Pros: regularly updated, allows point-of-care access to succinct indications or organ-specific antimicrobial recommendations Cons: requires navigation or search to obtain relevant information, must interpret with caution to applicability to local practice		
Sanford Guide Collection	Available as pocket books or individual APP purchase for electronic devices, relating to: Antimicrobial therapy, HIV/AIDS therapy, viral hepatitis therapy	$
Johns Hopkins Guides	Available as pocket books or in-APP purchases for electronic devices, relating to: Antibiotics, HIV	$
Bugs and Drugs	Available as individual APP purchase for electronic devices	$
Infectious disease-focused websites with easy to interpret disease- and treatment-related information Pros: regularly updated, provides succinct summary on disease, pathogens & treatment, information for the general public and healthcare professional can be found Cons: requires navigation or search to obtain relevant information, must interpret with caution to local practice		
World Health Organization	http://www.who.int/topics/infectious_diseases/en/	None
European Centre for Disease Prevention and Control	https://ecdc.europa.eu/en/home	None
U.S. Department of Health & Human Services, Centers for Disease Control and Prevention	https://www.cdc.gov/	None
Infectious Diseases Society of America	https://www.idsociety.org/Index.aspx	None
References for physician or specialist trainees practicing in infectious diseases Pros: provides in-depth learning opportunities regarding specific pathogens and diseases Cons: new editions with cost implication, nonpharmacy practice targeted		
Oxford Handbook of Infectious Disease and Microbiology	Available as printed pocket book, eBook or APP purchases for electronic device	$
The AST Handbook of Transplant Infections	Available as printed book or eBook	$
Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases	Available as 2-volume set printed book and eBook	$$$$
Feigin and Cherry's Textbook of Pediatric Infectious Diseases	Available as 2-volume set printed book and eBook	$$$$

In an outpatient setting, clinicians may prescribe a course of empiric therapy based on symptom and physical assessment to treat a clinically well patient with no imaging, laboratory, serologic or microbiologic workup. There may be times when outpatient workup should be considered. Suppose, an otherwise young healthy patient with no recent travel or hospitalization presents to her physician with dysuria, suprapubic pain, increased urinary frequency and urgency, but denies fever and flank pain. She may be diagnosed and prescribed treatment empirically for cystitis for which *Escherichia coli* (*E. coli*) is known to be the causative pathogen in over 75% of cases. Common references recommend trimethoprim-sulfamethoxazole (TMP-SMX) or nitrofurantoin but suggest local resistance patterns for *E. coli* should be confirmed to be <20% before prescribing TMP-SMX. After consulting a local antibiogram that documents ~75% susceptibility to TMP-SMX, a prescription for nitrofurantoin 100 mg PO BID for 5 days is written. If this same patient is currently in the third trimester of a pregnancy, treatment should be culture-directed and an end of treatment repeat culture should be done 1 week after the last dose of antibiotic. Some commonly used antimicrobials in the treatment of cystitis are not recommended due to risk to newborn (e.g., nitrofurantoin should be avoided due to risk of hemolytic anemia to the newborn).

Some patients with infections and significant comorbidities may require hospitalization for closer monitoring and management of exacerbations of chronic diseases. Hospitalization for a noninfectious cause should not result in an automatic escalation of antimicrobial therapy. These patients may still respond appropriately to the prescribed empiric course of antimicrobial based on an indication without further workup. Unfortunately, it is possible to develop new infections while hospitalized and for these patients the process of I.N.F.E.C.T.I.O.N.S. should be instituted for the new infection.

Culture Should Be Done in Clinically Relevant Specimens in Selected Patients

In some patients not improving on empiric therapy or if the patients present to the hospital with sepsis or septic shock, cultures may be required to ensure treatment is appropriate, as there are many noninfectious causes that may result in the same physiologic derangements. The criteria upon which sepsis and septic shock are diagnosed are listed in Table 25.4 [4]. Appropriate collection, processing, and interpretation of clinically relevant specimens allow confirmation of diagnosis and streamlining to definitive therapy. Such may be the case in an otherwise healthy individual who complains of a several-day history of fever and chills, increased difficulty in breathing, and fatigue that is on treatment with a respiratory fluoroquinolone, now presents with

Table 25.4 Sepsis and septic shock: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [4]

Terminology	Sepsis-3 definition	Diagnostic criteria
Sepsis	Life-threatening organ dysfunction caused by dysregulated host response to infection	Infection *plus* measure of organ dysfunction identified with: A raised sequential (sepsis-related) organ failure assessment score (SOFA), with a change in score of ≥2 from baseline or Quick SOFA (qSOFA) score considered positive if patient has ≥2 of the following clinical criteria: Respiratory rate ≥ 22 bpm Altered mentation, or Systolic blood pressure of 100 mmHg or less
Septic shock	Subset of sepsis with particularly profound circulatory, cellular, and metabolic abnormalities associated with substantially increased mortality	Vasopressor requirement to maintain a mean arterial pressure (MAP) of >65 mm Hg *and* serum lactate level > 2 mmol/L in the absence of hypovolemia The presence of both criteria predicts hospital mortality in excess of 40%

septic shock and specimens submitted for culture include blood, sputum, and urine. This patient has a radiographic evidence of pneumonia while history and urinalysis are negative for signs and symptoms of infection of the urinary tract. Suppose, the urine grew yeast, blood grew *Streptococcus pneumoniae*, and sputum grew *Streptococcus pneumoniae* and yeast. The yeast in urine is most likely insignificant as it reflects the result of antibiotic pressure from the recent use of a fluoroquinolone. The yeast in sputum is considered normal flora in respiratory tract but may be significant in immunocompromised patients which this patient is not. Of the cultures submitted, the significant pathogen most compatible with the presenting symptoms and adjunctive tests results is *Streptococcus pneumoniae*, which is known to be a respiratory pathogen.

In the absence of microbiologic sampling or where culture identifies presence of multiple organisms, a decision must be made based on the likelihood of an individual or group of organism's pathogenicity pertaining to the specific infection as well as its local susceptibility pattern.

Timing of First Antimicrobial Exposure Has Implications

Mortality

Debates continue to exist as to the optimal time to first dose of antibiotics. It was previously demonstrated that administration of an antimicrobial effective for the isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9% [5]. Each hour of delay over the next 6 h was associated with an average decrease in survival of 7.6% [5]. Yet, as more studies are conducted, data from larger trials where antimicrobial is evaluated as part of sepsis bundles, sensitivity analysis does not currently support a specific association between mortality and time to first dose of antibiotics. Most frontline clinicians, however, would agree that empiric therapy for patients in septic shock should not be unnecessarily delayed, despite knowing that antimicrobial naïve patient will typically generate the highest yield of causative pathogen from appropriate specimens collected. Therefore, in hemodynamically stable patients, cultures should be collected prior to first dose of antimicrobial.

Interpretation of Culture Results

Cultures should be interpreted within the framework of recent antimicrobial use. When antimicrobial is given before a blood culture that subsequently showed no growth, clinicians must interpret the significance of the negative result. Empiric narrowing of antimicrobials can be performed with caution after careful consideration of the negative result combined with an assessment of the most likely pathogen causing the presentation. The opposite is also true. A positive culture in a patient administered an antimicrobial usually effective against the organism may suggest difficult-to-eradicate pathogen due to its propensity to metastasize and seed in the body causing many foci of infection that must be drained, debrided, or resected. Alternately, it may suggest the need to optimize dosing regimens, reassess if the choice is appropriate for the site of infection, or consider the possibility of resistance.

Inquire into Allergies, Organ Functions, Genetic/Metabolic Abnormalities

Pharmacists are at a unique position to offer advice on antimicrobial therapy as the team member likely most knowledgeable in antimicrobials and their spectrum of activity. In practice, pharmacists are instrumental to ensure choice and dosing of medications are appropriate for patient-specific factors such as allergies and organ functions relevant to drug clearances.

Allergies and Intolerances

Some medical conditions, especially viral infections, can appear as exanthemata and in some cases, there is known association of high incidence of rash when an antibiotic (likely not indi-

Table 25.5 Beta-lactam antibiotics with similar side chains where cross-reaction between agents within a group is possible

β-Lactams with common R1 side chains at C-7						
Group 1		Group 2		Group 3		
Penicillin		Amoxicillin	Cefprozil	Cefepime	Cefpirome	
Cefoxitin		Ampicillin	Cephadrine	Cefetamet	Ceftizoxime	
Cephalothin		Cefaclor	Cephalexin	Cefeteram	Ceftpodoxime	
Cephalodrine		Cefadroxil	Ceftatrizine	Cefotaxime	Ceftriaxone	
β-Lactams with common R2 side chains at C-1						
Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Cefadroxil Cephalexin Cephradine	Cefmetazole Cefoperazone Cefotetan Cefamandole	Cefotaxime Cephalothin Cephapirin	Ceftibuten Ceftizoxime	Cefuroxime Cefoxitin	Cefdinir Cefixime	Aztreonam Ceftazidime Cefsulodin

Adapted from [6]

cated) is prescribed. For example, 70–100% of individuals with Epstein Barr virus mononucleosis-like syndrome treated with amoxicillin develop rash. For some patients, intolerances such as headache and gastrointestinal upset are reported as allergies. It is thus not surprising that up to 10% of the general population claims to have allergies to penicillin, with the actual frequency of anaphylactic-type reactions to penicillin closer to 0.01–0.05% [6]. Clinicians, including pharmacists, should elucidate the indication for the inciting antibiotic, timeline and evolution of any reaction, management for the reaction and if possible, a review of other antimicrobials given since. A patient with a true allergy to penicillin will be at risk of reaction to all penicillins. If a patient with reported penicillin allergy demonstrates tolerance to other penicillins (e.g., piperacillin-tazobactam), the patient should be counseled and have allergy de-labeled.

Cross-Reactivity Among Beta-Lactam Antimicrobials

From several studies conducted in the 1970s, cross-reactivity between penicillins and cephalosporins has been reported to be 7.7–8.1% and thus majority of literature quotes a cross-reactivity of <10% between the groups, whereas instances as high as 42% from early retrospective studies have been reported [7, 8]. More recent studies have demonstrated that the rate of cross-reactivity between the two groups is much lower than found in earlier studies (<1%) and appears to be driven by side-chain similarities between specific agents. Regardless of whether you can complete a detailed allergy assessment at the time of prescribing, it is important for pharmacists to be familiar with penicillins and cephalosporins with similar side chains as the presence of identical side chains is a factor contributing to cross-reactivity between penicillins and cephalosporins, in the range of 10–38% [9]. Cross-reactivity has been detected between ceftriaxone, cefotaxime, and cefepime, which share an identical side chain at the R1 position. However, it is overall hard to accurately predict the risk of cross-reactivity as some reactions may be due to antibodies to the common beta-lactam ring. With this in mind, Table 25.5 provides groupings of beta-lactam antibiotics that share similar side chains [6]. With regard to carbapenems, cross-reactivity among penicillins and carbapenems is estimated to be in the range of 1–4% [6, 9].

Sulfonamide Allergy

Nonantimicrobial sulfonamide allergy does not have implications on the prescribing of sulfonamide antimicrobials (e.g., TMP-SMX can be used in patients reporting allergy to sulfonamide diuretics). Most commonly, patients may report occurrence of maculopapular rash while on therapy. Where necessary, continuation of therapy to complete treatment may be tolerated. Alternatively, treatment may be held and a desensitization protocol can be used to

rechallenge these patients, often inducing tolerance [9].

Although less common than beta-lactam allergies, allergic reactions have been reported in all classes of antimicrobials. Mild cutaneous reaction where there is an absence of exfoliation of skin or involvement of mucosal and internal organs is commonly reported. Patients with severe cutaneous adverse reactions such as Steven-Johnson syndrome/toxic epidermal necrosis or drug rash with eosinophilia and systemic symptoms (DRESS), in general, should not be rechallenged and alternative therapy should be prescribed. Where no alternative exists, or where patient reports allergy to multiple classes of antimicrobials, referral to allergist may assist with defining the culprit.

Drug allergies and intolerances are significant barriers to prescribing the most efficacious therapy. With proper counseling, most patients will consent to being rechallenged with the inciting medications where mild reactions were reported or history of reaction is vague (e.g., childhood penicillin allergy where medical attention was not required to manage the reaction). Patient should be counseled to self-monitor and most ideally be closely observed.

Organ Function Relevant to Antimicrobial Therapy

Many antimicrobials require dosage adjustments for decreased renal and hepatic functions. For many renally cleared antimicrobials, dosage adjustments are range-based. For patients whose estimation of renal function (Cockcroft and Gault equation) lies on the cusp, it is useful to assess the overall trend of creatinine. If the trend portends improving renal function, the more aggressive dosing may be chosen with the exception of dialysis-dependent patients whose creatinine is artificially influenced by the dose of dialysis administered. Dialysis dosing guideline should be consulted for recommended adjustments based on the mode of dialysis employed. If a non-dialyzed patient with a renal function at steady state is lying on the cusp of dosing adjustments, an assessment of the risk and benefit of potentially overdosing versus inadequately treated infection may be required. In all cases, adjustments may also be indication and organ-specific. In jurisdictions where pharmacists may automatically adjust prescriptions based on organ function, prescribers should be encouraged to clearly indicate when dosing regimen is tailored to a specific indication or fluctuating renal function to avoid dosing errors.

Although some antimicrobials are cleared via liver metabolism, the dosage adjustments guidance is lacking for most. It is important to recognize that some antimicrobials should be avoided or used with caution in liver disease. When no alternative exists, close monitoring for adverse effects from antimicrobial therapy should be done while on therapy.

Genetic/Metabolic Characteristics Relevant to Antimicrobial Therapy

Although uncommon, specific genetic and metabolic characteristics can impact the choice and dosing of selected antimicrobials. Inappropriate choice and dosing can have serious implications. For example, prior to administering dapsone and primaquine, it is most ideal to check the glucose-6-phosphate dehydrogenase (G6PD) status of a patient as drug-induced acute hemolytic anemia can occur in individuals with G6PD deficiency. Dapsone is primarily used for treatment of leprosy, as an alternate in *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis, and also as part of second-line treatment for PCP. Consider checking G6PD status in patients deemed at risk of PCP as patients may develop adverse effects while on TMP-SMX, the preferred first line for both treatment and prophylaxis, and an alternative is required for continuation of treatment. Primaquine is currently the only available antirelapse therapy to cure the liver-stage infection and prevent relapse in malaria caused by *P. vivax* and *P. ovale*. It is also used as part of an alternative treatment in PCP for patients intolerant of TMP-SMX and dapsone. Malaria-specific tailoring of dosing recommendation for G6PD deficiency exists, and the drug can be administered with close monitoring for the prevention of relapses of *P. vivax* and *P. ovale* infections. Some clinicians may loosely adhere to this

Table 25.6 Example of an antibiogram

2017 Antibiogram	Cefazolin	Cloxacillin	Clindamycin	Tetracycline	TMP-SMX	Vancomycin
S. aureus—MRSA only	N/A	N/A	90[89]	99[89]	98[89]	100[89]
S. aureus—ALL	75[375]	75[375]	83[357]	97[354]	99[354]	100[384]
2014 Antibiogram						
S. aureus—MRSA only	N/A	N/A	69[87]	93[90]	97[89]	100[95]
S. aureus—ALL	71[332]	71[332]	80[307]	96[300]	97[311]	100[328]

% of isolates susceptible [# isolates tested], *MRSA* methicillin-resistant *Staphylococcus aureus*, *N/A* not applicable

recommendation as the trait of G6PD deficiency is highly prevalent particularly in people of African, Asian, and Mediterranean descent; however, it can affect all races although the severity of G6PD deficiency varies significantly among racial groups.

Consequences also exist for individuals with polymorphism in drug-metabolizing enzymes, in particular the cytochromes P450 (CYPs). This polymorphism is translated into risk differences concerning drugs metabolized by the highly polymorphic enzymes CYP2C9, CYP2C19, and CYP2D6. The resultant phenotypes include poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultra-rapid metabolizers. The most studied antimicrobial where polymorphism impacts the availability of active drug is voriconazole, where therapeutic drug monitoring of levels may be employed to guide dosage adjustments to ensure reasonable level is achieved. Discovery of the effects of genetic polymorphism on various medications, including antimicrobials, will continue to occur. Pharmacists should be aware of the impact and ameliorating strategies that can be utilized to enhance patient care.

Ongoing Assessment and Monitoring Required

Preliminary Results and Antibiogram

When an organism is isolated from a specimen, it is important to assess whether empiric therapy remains appropriate based on known local susceptibility data. While awaiting the susceptibility results specific to a patient's isolate, clinician can utilize the antibiogram to assess the probability of appropriate coverage with current therapy. Antibiogram offers an overall profile of antimicrobial susceptibility testing results of a specific microorganism to a panel of antimicrobials with reliable spectrum of activity in the literature. Based on the Clinical and Laboratory Standards Institute (CLSI) published guidelines, most North American and Canadian centers conduct annual compilation of data using only the first isolate per patient in the period analyzed and includes only organisms for which ≥30 isolates were tested. In addition to directing empiric antimicrobials while further susceptibility results are pending, it can also be used to detect and monitor trends in antimicrobial resistance as seen in Table 25.6. These data can be summarized at a ward, hospital or healthcare region level.

Although a useful tool, antibiograms should not be the sole deciding factor guiding therapy. The examples as shown in Table 25.6 would suggest that using vancomycin is likely 100% efficacious for treatment of *Staphylococcus aureus* infections. Based on cumulative clinical evidence, however, it is well known that beta-lactam exhibits a more rapid bactericidal activity [10]. In *S. aureus* bacteremia (SAB), rapid achievement or eradication is desired to minimize the metastatic manifestations such as infective endocarditis, polyarticular septic arthritis, vertebral osteomyelitis with or without paraspinal abscesses for which invasive source control may be required such as valve replacement, joint debridement, debridement of vertebral joint, or needle aspiration of abscesses. In patients with SAB, one acceptable approach may be to employ the strategy of concurrent usage of a narrow-spectrum beta-lactam and vancomycin until susceptibility is available. On the other hand, the same antibiogram would allow clinicians to confidently prescribe oral treatment for a patient with MRSA or MSSA skin abscess that required incision and drainage but is otherwise well and home-bound.

Clinical Monitoring

Patients should be assessed for clinical improvement or deterioration on a regular basis while on treatment. Changes in clinical status may be related to efficacy or toxicity. For example, clinical failure remains a possibility when an infection is caused by a pathogen capable of producing inducible resistance while on therapy (e.g., inducible AmpC beta lactamase *Enterobacter cloacae complex* treated with a cephalosporin). A patient may also develop reactions to the antimicrobial, which may have physical manifestations such as rash, vasculitis, etc.

Laboratory Monitoring

Ongoing assessment of bloodwork would also assist in monitoring for response and tolerance to therapy. Normalization of leukocytosis may suggest that the patient is responding to therapy. However, continual decrease of the white blood cell and development of neutropenia may suggest drug-associated adverse effects. An antimicrobial's adverse profile should be carefully reviewed and appropriate bloodwork ordered at regular intervals for assessment. Weekly or more frequent monitoring may be required if the patient is hospitalized for monitoring of infection or has fluctuating organ functions. For stable patients on long-term therapy, monitoring may be decreased to ≥ monthly at the discretion of the follow-up physician. Table 25.7 provides a general guide on laboratory monitoring for most commonly used antimicrobials as well as unique or common adverse effects to consider as part of monitoring. Additional laboratory monitoring and increased frequency of monitoring may be required for concomitant risk factors.

Table 25.7 Clinical and laboratory monitoring for commonly prescribed antimicrobials

	Laboratory monitoring (Frequency per Week)[a]					Clinical monitoring for adverse effects
	CBC & Diff	Cr ± BUN	Liver Enzymes	Electrolytes	Others	All patients should be counseled for self-monitoring of cutaneous, gastrointestinal adverse effects and anaphylactic/hypersensitivity reactions. Additional noninclusive clinical monitoring listed for common or significant adverse effects.
Antibiotics						
Aminoglycosides	1	2	1	–	–	Nephrotoxicity possible especially with concurrent risk factors. Cochlear and vestibular toxicity may be nonreversible and cumulative. Neuromuscular blockade has been described. Audiogram at regular interval recommended.
Beta-lactams	1	1	1	1	–	Most commonly associated with allergy reactions. Rare hematologic toxicity but increase with prolonged use. Beware of agent-specific adverse effects, e.g., penicillin-associated interstitial nephritis, myoclonic seizures with accumulation of inappropriately high dose.
Fluoroquinolones	1	1	1	–	–	Rare: hallucinations, psychosis, seizures, exacerbations of myasthenia gravis. Arthropathy with cartilage erosions maybe a concern in children; consider risk versus benefit. Tendinitis and rupture with concurrent risk factors. QT prolongation possible especially with concurrent risk factors.

(continued)

Table 25.7 (continued)

	Laboratory monitoring (Frequency per Week)[a]					Clinical monitoring for adverse effects
	CBC & Diff	Cr ± BUN	Liver Enzymes	Electrolytes	Others	All patients should be counseled for self-monitoring of cutaneous, gastrointestinal adverse effects and anaphylactic/hypersensitivity reactions. Additional noninclusive clinical monitoring listed for common or significant adverse effects.
Macrolides	1	–	1	–	–	Acute psychosis possible with clarithromycin. Reversible cholestatic hepatitis and hearing loss with azithromycin possible. QT prolongation possible especially with concurrent risk factors.
Tetracyclines	1	1	1	–	–	Photosensitivity-related rash and hyperpigmentation possible. Teeth/bone discoloration.
Miscellaneous antibiotics						
Chloramphenicol	1	1	1	–	–	Significant bone marrow suppression; fatal, aplastic anemia possible. Hemolytic anemia may be related to G6PD deficiency. Optic neuritis resulting in blindness possible.
Clindamycin	1	1	1	–	–	Transient transaminitis possible.
Daptomycin	1	1	1	–	CK weekly	Reversible skeletal muscle toxicity possible with >7 day use. Reversible eosinophilic pneumonia has been described with >10 day use.
Linezolid	1	1	1	–	–	Reversible myelosuppression (thrombocytopenia, pancytopenia) usually with use >2 weeks. Peripheral neuropathy and optic neuropathy may be permanent. Fatal lactic acidosis reported.
Metronidazole	1	1	1	–	–	Rare: seizures, encephalopathy, cerebellar dysfunction, and peripheral neuropathy, usually reversible. Disulfuram reaction with co-ingestion of alcohol.
Tigecycline	–	–	1	–	–	Significant dose-related GI side effects. Transient transamnitis possible.
TMP-SMX	1	1	–	1	–	Hyperkalemia, SJS, TEN, Sweet's syndrome. Drug-induced cholestasis and hepatitis possible.
Vancomycin	1	1	–	–	–	Reversible nephrotoxicty and ototoxicity (vertigo, tinnitus, hearing loss) possible especially with concurrent risk factors. Infusion-related reactions common including red man syndrome.
Antifungals						
Amphotericin B	1	2	1	2	Mg twice weekly	Infusion-related reactions may be minimized with reduced rate. Electrolytes abnormalities common. Nephrotoxicity common; reduced with lipid formulations and hydration.

Table 25.7 (continued)

	Laboratory monitoring (Frequency per Week)[a]					Clinical monitoring for adverse effects
	CBC & Diff	Cr ± BUN	Liver Enzymes	Electrolytes	Others	All patients should be counseled for self-monitoring of cutaneous, gastrointestinal adverse effects and anaphylactic/hypersensitivity reactions. Additional noninclusive clinical monitoring listed for common or significant adverse effects.
Azoles	1	1	1	–	–	Effect on QT interval, photosensitivity and visual disturbances may be agent-dependent. Potential for hepatic injury and rarely hepatic failure associated with all azoles.
Echinocandins	–	–	1	–	–	Infrequent and minor side effects. Adhere to infusion time recommendation to minimize histamine release-related symptoms (pruritus, facial swelling, vasodilatation).
Antivirals						
Acyclovir, valacyclcovir	1	1	1	–	Urinalysis weekly	Hydration and renally adjusted dosing to minimize accumulation associated neurotoxicity & nephrotoxicity.
Cidofovir	1	1	1	1	Urinalysis weekly	Dose-related nephrotoxicity, may be irreversible. Neutropenia common.
Foscarnet	1	2	1	2	Ca, Mg, Phos twice a week	Significant nephrotoxicity, usually reversible. Rarely: hallucinations and seizures. Adhere to infusion rate limits to minimize metabolic abnormalities; may result in arrhythmias, tetany, seizures.
Ganciclovir, valganciclovir	2	1	–	–	–	Significant reversible bone marrow suppression: leukopenia, neutropenia, thrombocytopenia. Confusion, psychosis, seizures, coma possible. Nephrotoxicity.

BUN blood urea nitrogen, *Ca* calcium, *CBC&Diff* complete blood count with differential, *CK* creatine kinase, *CR* serum creatinine, *GI* gastrointestinal, *Mg* magnesium, *SJS* Stevens-Johnson syndrome, *TEN* Toxic epidermal necrolysis
[a]Represents monitoring for 1. Therapeutic efficacy on leukocytosis 2. Hematologic toxicity 3. Renal or hepatic function for clearance of medication or potential toxicity. 4. Effects on electrolytes (potassium)

Narrowest-Spectrum Antimicrobial Should Be Used Whenever Possible and Applicable

Interpreting Patient-Specific Microbiologic Data

The ability to appropriately interpret microbiology data available empowers pharmacists to confidently assess indication as part of the patient care process. Astute examination of clinical signs and symptoms, microbiology data, combined with knowledge of the behavior inherent to an organism enables practitioners to differentiate between colonization and true infection. An example for interpretation of blood cultures is shown in Table 25.8.

Interpretation of other specimens may follow the similar process in assuring the result is relevant and interpret its impact on therapy. In most patients, for specimens that are suitable for Gram stain such as sputum or wound swabs, the presence or absence of white blood cells and bacteria may provide clues to the significance of subsequent growth. Suppose a patient is suspected to have developed a ventilator-associated pneumonia (VAP) from invasive ventilation required to

Table 25.8 Sample approach to interpretation of blood cultures: questions and implication in patient care

Is the culture antibiotic-influenced?
In the setting of recent or current use of antimicrobials: A negative blood culture may be representative of a false negative. A positive blood culture may indicate the need for source control, if applicable to a pathogen.
Is this collected from a line? If so, is there an accompanying peripheral blood culture?
If the patient has an existing intravenous line and, Growth from line specimen only ➔ blood culture from line with a corresponding negative peripheral blood culture may suggest line infection. Indication and duration of antimicrobial is dependent on source control and the identified organism. Growth from line and peripheral specimen ➔ differential time to positivity (dTTP) of ≥2 h may indicate catheter-associated bloodstream infection. A dTTP <2 h suggests bacteremia from other source. Growth from line specimen and no peripheral blood culture collected ➔ consider repeat blood culture from line *and* peripheral site before administering antimicrobial. Positive blood cultures from newly inserted lines (arterial or venous) generally represent true bacteremia from other source. To give clarity, repeat blood culture from line(s) and peripheral site before administering antimicrobial. Polymicrobial growth in blood culture may be line-associated or may represent contamination. In the right setting, polymicrobial growth supports the diagnosis and severity of a true infection where multiple organisms may translocate into the bloodstream, e.g. intraabdominal sepsis.
Preliminary identification based on morphology is available. Considering the history, exam, and presentation, what organism is the result suggestive of? Is there a need to modify empiric therapy?
Medically important organisms can be distinguished by their unique morphology. Preliminary results are commonly reported as: Gram-positive cocci in clumps may represent ➔ *Staphylococcal* species. Assess the likelihood of the pathogen based on history, exam, and presentation. Consider adding vancomycin if coagulase-negative *Staphylococcal* infection or if MRSA infection is a possibility. Gram-positive cocci in chains may represent ➔ *Streptococcal* or *Enterococcal* species. Assess the likelihood of the pathogen based on history, exam, and presentation. Consider adding vancomycin if *Enterococcal* infection is a possibility. Gram-negative bacilli ➔ Assess the likelihood of the potential pathogens based on history, exam, bloodwork, and presentation, e.g., symptoms of urinary tract infection, abdominal pain, etc. Broad-spectrum antimicrobials typically include adequate gram-negative coverage. In nonimproving and septic shock patient, consider adding a second agent for gram-negative coverage while awaiting final identification and susceptibility results.
How likely is this organism a contaminant based on assessment of existing risk factors and patients response to therapy?
Contamination may be likely if peripheral or line culture is positive in one vial out of many nonantibiotic-influenced specimens submitted. Interpretation will require knowledge of known specific pathogen's virulence or status as known colonizer on skin. In general, *Staphylococcus aureus* and yeast in blood should be viewed as true pathogens ➔ repeat blood culture and modify empiric therapy to ensure adequate coverage. Coagulase-negative *Staphylococcal* species may be pathogenic in appropriate settings (e.g. presence of prosthesis). However, it is the most common organism on human skin. If only one vial out of many is positive, the probability of contamination with this skin colonizer is high. This highlights the importance of repeating blood culture before starting therapy. It is important to note that one specific coagulase-negative *Staphylococcus*, *S. lugdunensis*, may cause serious infections, as usually seen for *Staphylococcus aureus*.

Table 25.8 (continued)

The organism has been identified and the susceptibility result is pending. Is there a need to modify empiric therapy? Are there further nonpharmacologic concerns that should be discussed with the team?
Modifications to empiric therapy can occur for selected organisms based on cumulative literature or information extracted from an antibiogram. For example, a patient presents with acute abdominal pain, with a several-day history of fever and chills, increased fatigue, and worsening nausea and vomiting. Admission bloodwork was within normal parameters and abdominal X-ray, chest X-ray (CXR), and CT abdomen were unremarkable. Patient was clinically stable and blood cultures were collected. No antibiotics were started. Overnight, therapy with meropenem was started for preliminary report of gram-negative bacilli growing in the submitted blood culture, which is subsequently identified as *Haemophilus influenzae*. You recall that *H. influenzae* is highly susceptible to third-generation cephalosporins and your institutional antibiogram confirms that in the previous year, 98% of isolates were susceptible to ceftriaxone and 68% to ampicillin. You recommended to your team to streamline patient to ceftriaxone at appropriate dose. Patient remains clinically stable. Your plan includes further narrowing to ampicillin, if this strain is beta-lactamase negative. However, you also notice that blood cultures collected after doses of meropenem were administered is still positive for GNB. In discussion with the attending physician, the possibility of endocarditis was discussed and echocardiogram was ordered. You also recall that your patient's past medical history includes documented hypogammaglobinemia, which may predispose this patient to invasive *H. influenzae* disease. You confirmed with local vaccination guidelines your patient should receive one dose of *H. influenza* b vaccination based on age and risk factor; however, your institution's policy is for patient to obtain vaccination as outpatient. During team rounds, the patient was updated with regard to the change in antimicrobial choice and inquiries made into tolerance to the medications. You document your interventions, discussion, and recommendation for vaccination at a later date.
Susceptibility has been reported. Can the antimicrobial be further streamlined to a narrow-spectrum antimicrobial?
Streamlining to the most effective therapy is safe even in patients who are critically ill when based on known pathogen and adequate source control where applicable. For example, a patient presents with signs and symptoms worrisome for necrotizing fasciitis. Blood culture was collected and patient was immediately taken for debridement of the affected areas. Broad-spectrum antimicrobial coverage with imipenem and vancomycin were started preoperatively. Intraoperative confirmation of diagnosis of necrotizing fasciitis was made. Over the next two days, patient underwent repeat debridement and remains mechanically ventilated and dependent on vasopressor but is slowly being weaned. Meanwhile, preliminary blood culture has shown gram-positive cocci (GPC) in chains, subsequently identified as *Streptococcus pyogenes*. Intraoperative wound tissue from debridement also shows GPC in chains. There is no microbiologic evidence to support polymicrobial infection. Can this patient be streamlined to penicillin and clindamycin as per guidelines for management of necrotizing fasciitis? Yes. *Streptococcus pyogenes* is exquisitely susceptible to penicillin with no reports of resistance globally. Clindamycin should be used concurrently to decrease the production of toxins. The slow clinical improvement is likely in response to the body's own response to the overwhelming infection and repeat iatrogenic trauma for source control. Unless there is evidence of a new or concurrent infection requiring broad-spectrum antimicrobial, continuation of the unnecessarily broad coverage does not offer advantage over narrowed-spectrum definitive therapy. Additional factor to consider in the setting of invasive group A streptococcal infection includes prescribing chemoprophylaxis for household or close contacts to the index patient.
Do we have documented clearance of the bacteremia? Is it required?
Due to heterogeneity of the causative pathogens in bacteremia as well as the impact of source control in its role to remove foci of persistent bacteremia, it is difficult to conduct well-designed trials to study the optimal duration of therapy. Current practice is largely driven by observational, retrospective data as well as expert opinions. Controversy exists regarding the importance of documented clearance of bacteremia. A potential for unnecessary invasive blood draw and resource consumption must be weighed against the consequence of unrecognized sustained bacteremia suggestive of need for further investigations, treatment, and may have implications on morbidity and mortality.
What additional information should be considered while finalizing a plan on choice, dose, and duration?
Confirm that chosen regimen is appropriate for indication, site of infection, organ function, and tolerance to antimicrobials. Clarify if antimicrobial should be intravenous or if oral therapy would be an option. Additional considerations include cost to patient if payment required or disposition may impact therapy.

support ruptured abdominal aortic aneurysm. A specimen was sent off for culture and a broad-spectrum antimicrobial was started (e.g., piperacillin-tazobactam). The Gram stain from the endotracheal tube sample shows high presence of polymorphs with predominance of gram-negative bacilli with the final identification of *Stenotrophomonas maltophilia* (a gram-negative bacillus) and coagulase-negative *Staphylococcus* (a gram-positive coccus). This patient will require modification of therapy to adequately treat *Stenotrophomonas* VAP. The coagulase-negative *Staphylococcus* does not require treatment if (1) there is no predominant growth shown on Gram stain and (2) it is unlikely to be a respiratory pathogen based on cumulative evidence. Exceptions will exist such as for severely neutropenic patients from chemotherapy treatment for leukemia or immunosuppressed patients post-transplant where the absence of leukocytes does not exclude the possibility of an infection.

Streamlining to Definitive Therapy

When patients are assessed in follow-up when the results of investigations and necessity and feasibility of source-control have been explored, and clinicians have the necessary information to finalize a therapeutic plan, streamlining to the narrowest-spectrum definitive therapy should occur. This should be done in a timely manner to minimize unnecessary exposure to broader than necessary antimicrobials.

Seamless Care

The finalized plan should be made based on reasonable clinical improvement along with a high confidence of obtaining the correct diagnosis with microbiologic data to support streamlining. This plan, including the choice, dosing regimen, duration of therapy, and monitoring plan should be clearly communicated to the patient. Pharmacists play an important role in counseling on the medications prescribed and to assess efficacy, tolerability, and ensure compliance. Additionally, pharmacists can maximize the future care of these patients by clear documentation of a patient's intolerance to an antimicrobial. It is especially important to document when desensitization or graded challenge was performed prior to a course of treatment with an antimicrobial that a patient is allergic to. Such information should be clearly communicated to patient as well as added to a patient's permanent medical records. As healthcare continues to work toward continuity of care, pharmacists' participation in seamless care will continue to evolve.

Clinical Pearls

- Encourage pre-antimicrobial microbiological sampling of suitable specimens when applicable to the practice setting and infectious diagnosis.
- Ensure empiric therapy is initiated for the suspected diagnosis based on common pathogens associated with specific infections with consideration of patient-specific risk factors.
- Participate in the follow-up of microbiologic, serologic, radiographic, and other diagnostic investigations or procedures performed to assess the impact on therapy.
- Anticipate and make recommendations on most appropriate definitive therapy based on culture and susceptibility results whenever possible or narrow coverage based on most-likely pathogenic organisms responsible when results are low-yield or when cultures are not performed.
- Participate in further reassessment and monitoring as required to ensure therapy is tolerated and resolution of the infection is achieved.
- Ensure the relevant team members and the patient are aware of the treatment and monitoring plans.
- Participate in allergy assessment and encourage de-labeling of allergies, when appropriate, or documentation of tolerance to antimicrobials for patients who report multiple allergies.

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Critical Care Assessment

26

Sherif Hanafy Mahmoud and Camille Yearwood

Chapter Objectives

1. Describe the role of the pharmacist in the intensive care unit (ICU) and in the care of critically ill patients
2. Describe the steps of critical care assessment, including collecting patient history, assessing the history of present illness, and conducting a review of systems
3. Apply knowledge of routes of administration, intravenous compatibility, and pharmacokinetic changes in the critically ill to ensure effective and safe medication delivery to the patient

Background

A critically ill patient is defined as a patient who has a life-threatening illness that often involves multisystem dysfunction and can result in morbidity and mortality. Generally, critically ill patients are cared for by an interprofessional team in the ICU. With the evolving role of pharmacists in clinical care, the presence of pharmacists in the critical care setting is becoming more common and presents a niche practice site for pharmacists. Pharmacist involvement in the care of the critically ill has been found to make a difference in patient outcomes [1]. For example, clinical pharmacy practice has been reported to result in improvements in fluid management and reduction in ventilator-associated pneumonia (VAP) occurrence, medication errors, and adverse drug reactions frequency [1]. As a result, pharmacists' presence in the ICU is the standard of care in Canada and the USA, and evidence demonstrating positive impact of pharmacy practice on ICU patient outcomes continues to emerge.

Critical care assessment incorporates aspects of a regular patient assessment, such as gathering a patient history, as well as speciality areas of assessment. Pharmacists in the ICU attend daily rounds with the interprofessional team where they can collect information on the patient's illness and status. An interprofessional team in the ICU usually consists of an intensivist, other specialists as required, a nursing team, pharmacist, respiratory therapist, dietician, physiotherapist, and social worker. Critical care assessment starts with data collection. The information from daily rounds and patient's chart can inform the pharmacist of the patient's history of present illness (HPI). Critically ill patients often have a more extensive HPI including microbiology and laboratory results, as well as other investigations such as diagnostic imaging. Once a complete HPI is collected, pharmacists conduct a review of systems, which focuses on medication-related

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inquiries and illness progression or improvement. For a critically ill patient, there are additional topics of assessment that are unique to this population. Due to the nature of these patients' illnesses, dose adjustments are often required due to drug interactions and pharmacokinetic changes. Critically ill patients may also need a route of administration assessment due to difficulties swallowing, feeding tubes insertion (e.g., nasogastric [NG] tubes), or lack of gastrointestinal access (e.g., nothing by mouth [NPO]). Intravenous (IV) lines are also common in this population and an investigation into IV compatibility may be necessary. Due to the instability and characteristics of ICU patients' illnesses, there can be medical concerns, such as a patient's acid-base balance or fluid status that also need to be assessed.

A critically ill patient's medications can be split into three categories including *d*isease-specific, *h*ospital-specific, and *p*atient-specific medications, which can be remembered by the acronym (DHP). Separating the medications into three separate categories allows for organization and can help ensure the pharmacist does not miss any aspect of a critically ill patient's medication assessment. Patient-specific medications are those that the patient had been prescribed and was taking before admission. Pharmacists have a role in identifying these medications through medication reconciliation and assessing the need to continue or discontinue the drug while the patient is critically ill. Disease-specific medications are those that have been initiated to treat the patient's current illness. Therapeutic drug monitoring (TDM) may be necessary with some disease-specific medications with narrow reference ranges. Hospital-specific medications are those that are not used to treat the patient's illness but may be required due to the patient's presence in the hospital. Pharmacists need to assess if a patient requires such medications, which can include deep vein thrombosis (DVT) and stress ulcer prophylaxis.

Pharmacists have an emerging role in the care of critically ill patients in the ICU and have been linked to improved clinical and patient outcomes. Critical care assessments need to be performed daily for each patient, as a patient's status can change quickly when critically ill. Knowledge of the speciality topics and specific skills required in critical care is necessary for any pharmacist pursuing a career in critical care.

Initial Assessment of a Critically Ill Patient

Past Medical History

Gathering the past medical history for the critically ill is quite similar to patients in the general population. This includes collecting the patient's demographics (age, sex, height, and weight), medical and medication histories, and allergies (see Chap. 1 for more details about patient history). In the ICU setting, patient information could be collected using the following sources:

- Patient or family: Patients in the ICU may be awake and able to provide and confirm their past medical history. However, given the nature of their critical illness, patients may be intubated or have altered mental status or level of consciousness (LOC) hindering their ability to provide such information. Hence, pharmacists will need to rely on other sources. The patient's family members may provide a reliable source of information depending on the patient's disclosure of healthcare information to his/her family or the family's involvement in the patient's previous healthcare.
- Patient's chart.
- Provincial electronic health record (EHR), e.g., NetCare
- Patient's healthcare providers in the community, e.g., family doctor
- Patient's community pharmacy

The patient's past medication history is essential information for the pharmacist. When collecting a patient's medication history, more steps are involved as the goal is to create the best possible medication history (BPMH), which is the first step in the medication reconciliation process. Medication reconciliation is the process

of ensuring that the most accurate medication information is collected and then each medication is reviewed and evaluated and either continued, changed, or discontinued/held. Medication reconciliation also involves communication with all members of the interprofessional team, so that there is consistency amongst the information available to each discipline. When conducting a medication reconciliation, the list of medications should be completed using more than one source. At least two sources are consulted as incorrect or incomplete information may be provided by any source. For example, on an EHR, it may show a medication that was dispensed by the pharmacy but was never actually taken by the patient or the patient may have received medication samples from a physician, which would not be reported on the EHR. The BPMH will result in a list of drugs that the patient was taking before admission, which can be referred to as patient-specific medications.

Patient-Specific Medications

Once the pharmacist is aware of the patient-specific medications, an assessment should be made to determine the indication for each drug. This can prove difficult due to the inability of the pharmacist to discuss with the patient. However, with the patient's past medical history, the pharmacist will likely be able to decipher the indication for most drugs. Due to the nature of the critical illness and possible hemodynamic instability of ICU patients, there are often drugs that can be temporarily discontinued while the patient is receiving this level of care. Examples of drugs that could be discontinued are bisphosphonates. The discontinuation of a bisphosphonate, while the patient is in the ICU, will not make a clinically significant difference in the patient's bone density but will decrease the number of drugs being administered to the patient. In addition, in the ICU, administering a drug can be more difficult due to presence of enteral feeding tubes or lack of gastrointestinal access. Continuing certain drugs can unnecessarily complicate patients' medication regimen and care, such as worrying about administering the bisphosphonate 30 minutes before food. Other medications may not be necessary for the patient to be taking in the ICU but require the pharmacist to contemplate the risks vs. benefits of discontinuation. For example, sudden discontinuation of antidepressants can cause withdrawal symptoms and the pharmacist should consider if this discomfort to the patient is outweighed by pill burden and possible drug-drug interactions. Finally, there are drugs that should be discontinued because they may cause harm to critically ill patients. For example, some patients in the ICU are at an increased risk of having acute kidney injury (AKI) due to factors such as renal hypoperfusion. Drugs that are nephrotoxic or may potentiate kidney injury may need to be discontinued. The pharmacist should still consider if discontinuing this drug will cause more harm than continuing it. Examples of medications that can cause kidney insult and may need to be held during an acute illness can be remembered by the acronym SADMANS. SADMANS stands for sulfonylureas, angiotensin-converting enzyme inhibitors (ACEIs), diuretics, metformin, angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), and sodium-glucose linked transporter 2 (SGLT2) inhibitors. Note that this is just an example of some drugs that should be assessed for discontinuation. There are exceptions as drugs such as diuretics are used in the ICU setting, while a drug such as metformin would rarely be continued in an unstable patient. As part of an interprofessional team providing care to critically ill patients, conducting assessment to continue or discontinue patient-specific medications is a role that pharmacists can take lead. A medication reconciliation to create a BPMH should be completed on admission, at any transition of care (e.g., when a patient is moved to another unit in the hospital), and at discharge as this minimizes the chance for medication errors and promotes seamless care.

History of Present Illness

After the pharmacist has collected patient history, the next step is to determine the reason of admission and history of present illness (HPI). Some common reasons for admission include

sepsis, traumatic brain injury (TBI), shock, trauma, and respiratory failure. Once the HPI and the patient's current status is known, the pharmacist can begin to assess the patient's disease-specific medications for indication, efficacy, and adverse effects.

Disease-Specific Medications

Disease-specific medications are drugs that are used to treat the patient's current illness. These drugs will be individual to the patient and his/her illness. Pharmacists should refer to the disease-specific clinical guidelines or the best evidence available to inform their treatment decisions. In addition, there are classes of drugs that are commonly seen in the ICU such as those needed to treat the patient's condition and/or hemodynamic instability that critical care pharmacists need to be familiar with. These include sedatives, analgesics, vasopressors, and antimicrobials. Table 26.1 provides a summary of the common medications used in the ICU. Pharmacists assess the suitability of the current patient-specific medications to ensure they are safe, effective, and indicated.

Hospital-Specific Medications

Hospital-specific medications are medications used to prevent complications that patients may experience due to the fact that they are in a hospital. Hospital-specific medications are not the drugs that the patient was previously on before admission and are not the ones that are used to currently treat the patient's reason for admission illness. These medications may often be overlooked due to the focus on disease-specific medications that are used to treat the patient's current illness. Therefore, pharmacists can have a significant role in assessing the patients' need for hospital-specific medications. Those medications should be assessed daily as the need to continue these medications can change throughout the patient's hospital stay. Hospital-specific medications can be unintentionally and unnecessarily continued in some patients during their transition of care, and pharmacists can prevent this by completing a medication reconciliation at each care transition and at discharge.

Table 26.1 Examples of common medications utilized in the intensive care unit

Drug class	Example
Vasopressors and inotropes	Epinephrine, norepinephrine, dobutamine, dopamine, vasopressin, phenylephrine, milrinone
Vasodilators	Sodium nitroprusside, labetalol, hydralazine, nicardipine, nitroglycerin
Sedatives and anesthetics	Propofol, midazolam, ketamine Dexmedetomidine
Opioid analgesics	Fentanyl, hydromorphone, fentanyl
Neuromuscular blockers	Succinylcholine; cisatracurium, rocuronium
Antiarrhythmic	Amiodarone, diltiazem, lidocaine

DVT Prophylaxis

Pharmacists should determine for every patient in the ICU if DVT prophylaxis is appropriate. The pharmacist should assess the patient's risk of experiencing a DVT before deciding to initiate prophylaxis therapy. Critically ill patients require DVT prophylaxis more often than other patient populations due to factors related to their illness. DVT risk factors include the expected length of stay, degree of mobilization, surgery and type of surgery, and age. A longer length of stay increases the risk of a DVT. Patients who are immobile have a greater DVT risk due to the pooling of blood in their legs. Surgery is a risk factor due to immobilization during and after surgery and it can result in damage to patients' vasculature. In addition, the length of surgery correlates with a higher risk for development of DVT as the longer the surgery the longer the patient was immobilized for on the operating table. The type of surgery can also increase the risk for DVT. Surgeries with increased risk are those that require arteries and veins to be cut and repaired. Critically ill patients have multiple risk factors and often qualify for DVT prophylaxis. However, the pharmacist must also

Table 26.2 Recommended DVT prophylaxis dose in select anticoagulants

Drug class	Drug	Recommended prophylactic dose
Low molecular weight heparins	Dalteparin	5000 units subcutaneously once daily
	Enoxaparin	40 mg subcutaneously once daily or 30 mg subcutaneously twice daily
	Tinzaparin	4500 units subcutaneously once daily
Unfractionated heparin	Heparin	5000 units subcutaneously every 12 hours OR every 8 hours

DVT deep vein thrombosis. Note: Above dosing might vary based on patient-specific characteristics

consider the patient's bleed risk and conduct a benefit vs. risk analysis to determine if pharmacological prophylaxis is appropriate. If the patient is unable to receive pharmacological DVT prophylaxis due to, for example, an active bleed, nonpharmacological DVT prophylaxis such as pneumatic compression stockings can be used. However, they are not as effective at DVT prevention compared to pharmacological therapy. Therefore, a reassessment of the patient's conditions should occur daily as he/she should be switched to a pharmacological alternative as soon as it deems appropriate. Table 26.2 depicts examples of anticoagulants and their prophylaxis dosing. The choice of the agent and its dosing depends on patient-specific characteristics (e.g., weight, renal function) and the evidence supporting their use in certain patient populations.

Stress Ulcer Prophylaxis (SUP)

A stress ulcer is a gastric mucosal erosion that breaches the submucosa and puts the patient at a high risk for gastrointestinal bleeding. Stress ulcers generally result from ischemia secondary to reduced gastric blood flow, followed by reperfusion injury. Gastrointestinal bleeding can cause morbidity and at a minimum, a four-fold increase in ICU mortality [2]. Critically ill patients are at an increased risk of developing a stress ulcer due to the possible coexistence of multiple risk factors (Table 26.3). The patients at the highest risk for gastrointestinal bleeding are those with mechanical ventilation >48 hours and those with coagulopathy [2]. The need for stress ulcer prophylactic therapy should be assessed for each patient and the presence of one or more risk factors may indicate the need to start therapy. Drugs used as prophylactic therapy include histamine-2 receptor blockers (H_2RBs) and proton pump inhibitors (PPIs). However, the benefit of SUP in critically ill patients has been put into question with recent evidence suggesting that PPI could have no benefit in critically patients with early enteral nutrition [3]. In addition, increasing the gastric pH secondary to SUP may increase the risk of ventilator-associated pneumonias and *Clostridium difficile* infections [2]. Due to the potential risk of complication associated with prophylaxis, the pharmacist should assess the need for prophylaxis on a case-by-case basis and consider both the benefits and risks for each patient. In addition, the pharmacist should assess if prophylactic therapy requires continuation throughout the patient's stay in the ICU.

Table 26.3 Risk factors for development of a stress ulcer in the ICU

Mechanical ventilation >48 hours	History of GI ulceration or bleeding within 1 year
Requirement of high dose steroids	ICU stay ≥1 week
Coagulopathy	Major surgery lasting >4 hours
Multiple trauma/ traumatic brain injury	Acute lung injury
Acute kidney injury	Hepatic dysfunction
Sepsis	Hypotension

ICU intensive care unit, *GI* gastrointestinal

Bowel Routine

Constipation is one of the common complications in the ICU. Critically ill patients have an increased risk of developing constipation secondary to multiple risk factors related to their medications and their illnesses:

- Medication-induced constipation, e.g., sedatives, opioids, and 5-HT_3 receptor antagonists
- Reduced food intake secondary to poor appetite, reduced fiber intake, and/or reduced oral intake, e.g., NPO
- Decreased mobility/surgery: Decreased mobility and surgery are also considered risk factors for constipation. Critical care patients are often confined to their beds due to their illnesses or due to immobilization during or after surgery.
- Metabolic disturbance, e.g., dehydration and renal failure
- Presence of neurological disorders such as spinal cord injury

Constipation in the ICU, if untreated, may result in multiple complications that could result in longer ICU stay and increased patient morbidity. These complications include poor tolerance to feeds, poor nutrition, gastroparesis, and increased intra-abdominal pressure leading to decreased lung compliance in ventilated patients and difficulty weaning. A bowel routine is used in the hospital to prevent or treat constipation. All patients should be assessed if bowel routine is appropriate. The drugs most often prescribed are polyethylene glycol 3350, lactulose, sennosides, bisacodyl, or a combination. These drugs can be prescribed on an as needed basis or as regularly scheduled dosing. Pharmacists should assess the continued need for these laxatives daily by consulting with the patient's nurse(s) or chart. They assess if the patient is having regular bowel movements, diarrhea, or constipation. Based on this assessment, the laxatives may be continued, discontinued, have a dose change, or be switched to an alternative regimen.

Daily Assessment

In contrast to other patient populations, critically ill patients' clinical status might change quickly throughout their ICU stay. As a result, following the initial assessment, ICU pharmacists should assess their patients daily to determine if a change in plans is needed. The daily assessment performed for each patient is quite comprehensive and involves a review of systems and review of patients' microbiological tests, laboratory tests, other investigations, and current medications. Daily assessment data are generally obtained from the daily multidisciplinary rounds, where the bedside nurse provides a detailed report of the patient's progress in a head-to-toe approach. As mentioned previously, other sources of information include the patient interview (if possible), patient's chart, and EHR. A review of systems is a methodical approach to assessing patients' current clinical status and is grouped into assessment by individual organ systems. Pharmacists may not be the healthcare professionals conducting the physical assessment on the patient, but they should be able to interpret the findings of the assessment and apply it to their patient care. Similar to the initial assessment, pharmacists should also conduct a review of the patient's medications (patient-specific, disease-specific, and hospital-specific) on a daily basis. The appropriateness of a drug therapy can change quickly in critically ill patients and drugs may need to be initiated and discontinued or dose adjustments may be required. A generalized overview of a daily assessment of a critically ill patient by a pharmacist is presented in Table 26.4.

Review of Systems

The main organ systems that will be the focus of this chapter are the central nervous system, cardiovascular, respiratory, gastrointestinal, and genitourinary.

Central Nervous System (CNS)

Assessment of patients' level of consciousness (LOC) is essential in critical care assessment. The most common scale for determining a patient's level of consciousness that is performed at the bedside is the Glasgow Coma Scale (GCS) (see Chap. 3 "Physical Assessment for Pharmacists"). LOC might reflect the severity of the patient illness, degree of sedation, and/or adverse effects of medications. In addition,

Table 26.4 Pharmacist's checklist of daily assessment of critically ill patients

Assessment category	Monitoring parameters
Central nervous system (CNS)	Level of consciousness (GCS) Presence of delirium Degree of sedation Pain control
Cardiovascular system (CV)	Blood pressure (SBP, DBP) Blood pressure target Heart rate and rhythm Presence of arrhythmias QTc interval T_{max} in the last 24 hours Fluid status IV fluids administered Need for vasoactive agents (vasopressors and/or inotropes) Need for antihypertensive therapy Need for DVT prophylaxis
Respiratory system (RESP)	Respiratory sounds Respiratory rate ABGs Acid-Base balance Respiratory secretions Infection (e.g., pneumonia) Presence of mechanical ventilation and ventilation parameters
Gastrointestinal system (GI)	Feeding status (e.g., DAT, oral intake, feeding through enteral feeding tube, NPO) Tube feed tolerance Any nausea or vomiting Need for stress ulcer prophylaxis Bowel sounds Presence of constipation or diarrhea Need for bowel routine Hepatic function
Genitourinary system (GU)	Urine output Fluid balance Renal function Infection (e.g., UTI) Acid-base balance
Microbiology (micro)	Risk of infection or presence of infection Cultures and sensitivities Need for cultures Appropriateness of the antimicrobials Therapeutic drug monitoring
Labs	Check relevant labs regularly Check the trend of lab values (more informative than single values) Adjust drugs or drug dosages as appropriate
Other investigations	Check for new investigations daily Includes exploratory tests and diagnostic imaging
Medications	Patient-specific medications Hospital-specific medications Disease-specific medications Need for dosage adjustments Assessment for the need of PRN medications Drug interactions Intravenous compatibility

ABGs arterial blood gases, *DAT* diet as tolerated, *DBP* diastolic blood pressure, *DVT* deep vein thrombosis, *GCS* Glasgow Coma Scale, *MAP* mean arterial pressure, *NPO* nothing by mouth, *PRN* when needed, *SBP* systolic blood pressure, *UTI* urinary tract infection

changes in LOC provide an insight on patient progress. For example, sudden GCS changes in patients with subarachnoid hemorrhage (SAH) might indicate the development of delayed cerebral ischemia, a common complication following SAH. In addition, patients that are unconscious or comatose will have a feeding tube and will require an assessment of their drugs to determine if they can be administered through a feeding tube. More information regarding drugs and feeding tubes can be found under the section "Routes of Administration."

In the ICU, patients are at risk of developing delirium due to their illness (e.g., infections, organs failure) and the medications they are getting. Delirium is defined as a disturbance in mental function and a reduced awareness of the environment. Delirium can present as confusion, disorientation, and a decreased level of alertness. Delirium is often transient, but in the ICU population, it is associated with long-term cognitive dysfunction, increased mortality, and prolonged ICU stay [4]. The presence of delirium can be determined with the use of the Confusion Assessment Method for the ICU (CAM-ICU) or with the use of the Intensive Care Delirium Screening Checklist (ICDSC). Pharmacists should be aware if a patient is experiencing delirium as it can be caused by drugs and will require an assessment to determine if a drug is an instigating factor. Some of the drugs that are associated with causing delirium include sedative hypnotics, such as benzodiazepines and narcotic analgesics. In patients experiencing delirium, assessment for alternative therapeutic options with less propensity in causing delirium is recommended. Delirium can be treated with the use of atypical antipsychotics such as quetiapine and haloperidol. Nonpharmacological modalities include promoting good sleep habits, ensuring the patient is well hydrated, and improving the patient's sensory input through devices such as hearing aids [4].

Sedation is another part of the CNS assessment in the ICU. Sedation of critically ill patients improves tube tolerance and mechanical ventilation optimization in intubated patients. In addition, it helps control agitation, reduces oxygen consumption, and reduces intracranial pressure (ICP). The Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS) can be used to assess a patient's degree of sedation. It is generally recommended that sedative drugs be used to maintain a light level of sedation (RASS of −2 or higher). Light sedation in this population is associated with improved clinical outcomes, such as a shorter ICU length of stay [5]. Table 26.1 depicts examples of common sedatives in the ICU. Level of sedation required might need to be changed based on the patient condition or progress. For examples, TBI patients with elevated ICP might require higher level of sedation compared to general critically ill patients.

Another element in CNS review is pain and pain control. Sometimes pain assessment can be challenging in the critically ill as many patients are unable to report if they are experiencing pain. There are scales developed to help assess a patient who is unable to provide verbal information, such as the Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT). Note that for these scales to be valid, the patient has to have intact motor function [5]. Vital signs can also be used to assess for the presence of pain with an increase in blood pressure, heart rate, respiratory rate, and increase in body temperature signifying the patient may be in pain. However, vital signs should not be the sole aspect of pain assessment and should be only used with a validated pain assessment scale [5]. Opioid analgesics such as morphine, hydromorphone, and fentanyl are considered the first-line therapy options in critically ill patients. However, nonopioid analgesics such as NSAIDs and acetaminophen should also be considered to decrease the amount of opioid being administered to the patient to decrease the risk of delirium or other adverse effects, such as constipation [5].

Cardiovascular System (CV)

It is important to closely and frequently monitor cardiovascular system function. It is useful to assess hemodynamic stability, disease severity, organs perfusion, response to therapies, adverse

effects of medications and/or need for additional therapies. The following values should be assessed regularly:

- Maximum temperature within the last 24 hours (T_{max})
- Blood pressure (SBP and DBP) and mean arterial pressure (MAP). MAP is useful as it approximates organ perfusion. In the ICU, the target MAP for most patients is ≥65 mmHg [6]. Eq. 26.1 depicts how patient's MAP is calculated.

$$\text{MAP} = ((2 \times \text{diastolic blood pressure}) + \text{systolic blood pressure} \div 3) \quad (26.1)$$

- Blood pressure target: BP target is disease-specific and will need to be determined on an individual basis.
- Central venous pressure (CVP): CVP is the blood pressure in the venae cava near the right atrium. It can be used in the ICU to monitor the patient's fluid status, as it reflects the amount of blood returning to the heart.
- Heart rate and rhythm: Patients are also continuously monitored with an electrocardiogram (ECG). This allows monitoring for heart rate and rhythm and allows detection of cardiac arrythmias such as supraventricular tachycardia, atrial fibrillation, and ventricular tachycardia. In addition, QTc interval monitoring could be obtained which is helpful in the presence of interacting drugs that cause QTc interval prolongation. Cardiac arrhythmias can be very serious and can cause mortality and need to be addressed and treated immediately.
- Need for vasopressors (see Table 26.1) as in cases of shock (see below).
- Need for antihypertensives: In the ICU, patients can also experience a hypertensive crisis, which is defined as a systolic blood pressure ≥180 mmHg or a diastolic blood pressure ≥120 mmHg. Hypertensive emergencies are also associated with morbidity and mortality and are often treated with drugs such as sodium nitroprusside or labetalol (see Table 26.1).
- Some laboratory values and investigations (discussed later) can be interpreted in concert with above assessment. For example, lactate can be used to identify if the patient is hypoxic and a value >1 mmol/L is a sign that the patient is not getting a sufficient level of oxygen to the tissues.

Shock

Shock is the most common manifestation of circulatory dysfunction in the ICU and is a serious condition in which there is not enough blood flow to the other organs of the body. There are four types of shock:

- *Hypovolemic shock*, which is caused by insufficient blood volume due to loss of fluid from circulation.
- *Cardiogenic shock* is due to the inability of the heart to pump blood effectively and can be caused by conditions such as myocardial infarction or heart failure.
- *Obstructive shock* is due to obstruction of blood flow outside of the heart in conditions such as pulmonary embolism.
- *Distributive shock* is due to an abnormal distribution of blood flow due to vasodilation and can be caused by sepsis (septic shock), anaphylaxis, or spinal injuries (neurogenic shock).

Patients in shock often receive fluid resuscitation and inotrope agents and/or vasopressors. Inotropes are used to increase a patient's cardiac output, therefore increasing MAP and allowing the organs to maintain perfusion. Vasopressors cause vasoconstriction to increase the patient's MAP (see Table 26.1).

Respiratory System

Critically ill patients require close monitoring of their respiratory system as many require oxygen and potential mechanical ventilation. In daily rounds, generally, the respiratory therapist provides the progress report of the patient's respiratory status. Respiratory status includes respiratory rate, respiratory sounds, ventilation parameters (if applicable), quality, and quantity of respiratory secretions and arterial blood gases. These are also interpreted in concert with other laboratory values pertaining to acid-base balance (later

discussed in this chapter), chest X-ray (CXR), and sputum cultures. Respiratory tract infections are also of concern in patients in the ICU and can be detected through presence of respiratory distress (abnormal ABGs), hypotension, mental status changes, difficulty weaning from mechanical ventilation, and CXR. Respiratory secretions are often purulent, and a sputum sample should be cultured to determine the responsible pathogen.

Arterial Blood Gases

Laboratory tests that are used for monitoring of respiratory function include measuring arterial blood gases (ABGs). An ABG test measures:

- *Partial pressure of oxygen (PaO_2)*, which is a measure of the pressure of oxygen dissolved in the blood and how well the oxygen can move from the lungs into the blood. A low PaO_2 indicates the patient is not oxygenating properly and is hypoxemic.
- *Partial pressure of carbon dioxide ($PaCO_2$)*, which is a measure of the pressure of carbon dioxide dissolved in the blood and how well the carbon dioxide is moving out of the body.
- *pH* measures hydrogen ions (H^+) in a patient's blood. A low pH is an indicator of acidemia and a high pH is an indicator of alkalemia.
- *Bicarbonate (HCO_3^-)* is used as a buffer to counteract pH changes if the blood is too acidic or basic. A low HCO3- level indicates metabolic acidosis, and a high HCO3- level indicates metabolic alkalosis.
- *Oxygen saturation (SaO_2)* measures how much hemoglobin is carrying oxygen. SaO2 can also be calculated with pulse oximetry.

Fraction of Inspired Oxygen (FiO_2)

FiO_2 is the fraction of oxygen in the volume of air inspired and is a measure of the percentage of oxygen participating in gas exchange in the lungs. FiO_2 is used in the calculation PaO_2/FiO_2 ratio and is used as a measure of oxygenation. PaO_2 should increase with increasing FiO_2 and a decrease in the ratio indicates inadequate or decreased oxygen exchange or hypoxemia. The ratio can be used to determine the amount of oxygen that will be delivered to the patient in the form of oxygen-enriched air. A normal PaO_2/FiO_2 is >400 mmHg, a PaO_2/FiO_2 ratio ≤300 mmHg indicates acute lung injury, and a PaO_2/FiO_2 ≤200 mmHg is indicative of acute respiratory distress syndrome (ARDS) [7]. ARDS is a respiratory failure with rapid onset of lung inflammation and the inability of the lungs to effectively provide oxygen to the rest of the body or expire carbon dioxide out of the lungs [7]. Most patients with ARDS will require mechanical ventilation. Risk factors include pneumonia, sepsis, and severe trauma. CXR is also used to detect the presence of ARDS or monitor its progression.

Mechanical Ventilation

Mechanical ventilation is common in the critically ill patient population. Although pharmacists are not involved in determining the ventilation parameters, patients' current parameters can inform the pharmacist if the patient is doing better or worse. There are three main stages of mechanical ventilation. The first is the trigger, which is the signal that initiates opening of the respiratory valve. The next is the limit which regulates gas flow into the lungs and finally cycling which stops the inspiratory phase and leads to opening of the expiratory valve. There are also three methods of cycling from the inspiratory to expiratory phase:

- Volume cycled – delivers a preset volume of gas into patients' lungs as the inspiratory phase begins, and once this volume is reached, the patient passively exhales. This is the most common type of ventilation cycling.
- Pressure cycled – gas flows into a patient's lungs when the inspiratory phase begins until a pressure-sensing mechanism reaches a preset level and the patient passively exhales.
- Time cycled – gas flows into a patient's lungs when the inspiratory phase begins until a timing mechanism reaches a preset duration and the patient passively exhales.

There are also different modes of mechanical ventilation and include control modes or support modes. In pressure control ventilation, the respiratory rate is set, and the gas is delivered nons-

pontaneously. This method is used primarily in patients that are not conscious or are under more sedation. Pressure support allows the patient to trigger the ventilation with a preset pressure assistance delivered with each breath to decrease the work of breathing. In this mode, the patient controls the respiratory rate, duration of inspiration, and tidal volume.

Pharmacists can monitor the status of patients with the use of ventilation parameters. There are four main parameters that the pharmacist can look at:

- Tidal volume: The volume of air inhaled or passively exhaled in a normal respiratory cycle. The tidal volume that is set is often dependent on patient characteristics such as lean body weight and their disease.
- Respiratory rate: The number of preset tidal volume breaths of the patient will be received from the ventilator. If the patient is on support ventilation, the patient can also spontaneously breathe above the set rate.
- FiO2: See above. An increase in this value signifies deterioration.
- Positive End Expiratory Pressure (PEEP): Maintains pressure in the lungs during exhalation phase and improves oxygenation by enhancing alveolar volume and increasing oxygen exchange through an increase in surface area.

Gastrointestinal System (GI)

Daily gastrointestinal (GI) assessment is essential for proper critical care assessment as it might influence the choice and dosage of drug regimens. The feeding status of every patient should be determined. While some patients might be awake and able to swallow and on diet as tolerated (DAT), others are getting nutrition through feeding tubes, e.g., nasogastric (NG) or OG (orogastric). See section "Routes of Administration" for further details on how this might affect pharmacist's decisions on drug therapies. Altered drug absorption might also be present in critically ill patients secondary to multiple factors such as delayed gastric emptying, binding to feeds and vasopressor use. This should be taken into consideration when assessing the efficacy of orally administered medications. Other GI assessment considerations include the need for stress ulcer prophylaxis and bowel routine; tube feed tolerance; presence of GI symptoms such as nausea, vomiting, diarrhea, or constipation; and assessment of bowel sounds.

Bowel sounds are caused by the movement of the intestines as food is passed through the gastrointestinal tract and are detected with the use of a stethoscope. Reduced bowel sounds indicated that there is decreased intestinal activity, and this can indicate constipation. The absence of bowel sounds can indicate an ileus which is a condition where there is a lack of intestinal movement, and this can lead to complications such as intestinal obstruction. There are times of the day where reduced bowel sounds are normal, such as during sleep. Hyperactive bowel sounds or an increase in intestinal activity can occur with diarrhea or directly after eating. The assessment of bowel sounds should also be accompanied by assessing patients' bowel movements.

Genitourinary System

Assessment of patients' renal function is essential for pharmacists as it helps guiding dosage adjustment of renally eliminated medications. In addition, it affects therapy decisions in terms of choice of non-nephrotoxic medications in patients with renal impairment. Renal function can be assessed through laboratory tests, e.g., serum creatinine and blood urea nitrogen in conjunction with patient's urine output. Normal urine output for an adult is 0.5–1 ml/kg/hr. Critically ill patients are at an increased risk for the development of AKI, and the diagnosis of AKI relies on a decreased urine output and increased SCr and BUN. If AKI occurs, the pharmacist should assess a patient's drugs and discontinue nephrotoxic drugs, if possible. See Chap. 24 for further information regarding renal function assessment.

Fluid balance is also an important factor to monitor in critically ill patients. Hypovolemia can lead to low organ perfusion and decreased oxygenation to the tissues and hypervolemia can lead to organ damage and conditions such as pulmonary edema. Maintaining a euvolemic fluid balance is required to prevent complications. Urine output can be used as an indicator of abnor-

mal fluid balance either by reflecting polyuria or oliguria. Correcting an abnormal balance may include fluid administration in hypovolemia or the use of diuretics in hypervolemia. Abnormal fluid balance can also cause electrolyte disturbances, which can be dangerous and require correction. It can also cause acid-base imbalances, and this can be monitored through ABG tests. Refer to the section "Acid-Base Balance" for more information.

Patients in the ICU are also at an increased risk for urinary tract infections (UTIs) secondary to multiple risk factors such as urinary catheterization and immunosuppression and should be monitored. Some signs and symptoms of a UTI can include pyrexia, mental confusion or altered mental status, and dysuria. The urine should be cultured, and antimicrobial therapy might be required.

Microbiology

Sepsis is one of the main reasons of ICU admission [8]. In addition, critically ill patients are also at an increased risk for the development of nosocomial infections due to being immunocompromised or because of the multiple points of entry for bacteria. ICU patients often have catheters, IV lines, and could be on mechanical ventilation. Examples of those infections include VAP and catheter-associated urinary tract infections. Pharmacists have an important role in assuring that critically ill patients are prescribed appropriate antimicrobials with an appropriate dosage regimen throughout patients' ICU stay. Initiation of effective antimicrobials within the first hour after development of hypotension has been associated with increased survival in patients with septic shock [9]. Due to the severity of infections in critically ill patients and the need for quick initiation of antimicrobials, often it is not possible to wait for the results of cultures and empiric therapy is required. Once the initial culture is back, pharmacists should step down the empiric therapy to the appropriate targeted antibiotic therapy to prevent unnecessary drug use. Continued empiric therapy puts the patient at an increased risk for adverse effects, drug interactions, and the development of antibiotic resistance. Pharmacists should keep in mind that in the ICU there can be changes in susceptibilities and resistance patterns and should always consult the site-specific antibiogram. Pharmacists should continue to follow-up with cultures and sensitivities daily and order cultures when appropriate. They should also be aware of the normal flora in culture media that are less likely to be pathogenic to avoid unnecessary use of antimicrobials. For example, the presence of *Candida* in sputum cultures generally does not need to be treated. TDM can also be required for some antimicrobials, for example vancomycin and aminoglycosides. Pharmacists have a role to identify which patients should receive TDM, monitor the drug levels throughout, and make appropriate dose adjustments based on the results. For more information on infectious diseases assessment, the reader can refer to Chap. 25 "Infectious Disease Assessment."

Labs

Critically ill patients are often hemodynamically unstable, mechanically ventilated, on multiple pharmacological and nonpharmacological interventions that might result in rapid changes in their status and organ function throughout their ICU stay. As a result, ICU patients have daily lab tests done or even multiple times throughout the day. Pharmacists should regularly check patients' lab values to monitor response to therapies, adverse drug reactions, and organ functions and to assess the need of further management. For example, a patient's renal function can change rapidly due to an AKI and pharmacists must be aware of the patient's current kidney function so that they can dose the patient's medications appropriately. Pharmacists can also order additional lab tests to ensure that they get the information required to complete an informed assessment or to monitor the patient. Table 26.5 provides some of the lab tests that may be ordered in the ICU for monitoring critically ill patients. Abnormal values may indicate an underlying pathology and can lead to serious complications and should always be investigated.

Table 26.5 Common lab tests that are ordered in the ICU

Category	Examples
Electrolytes	Sodium, potassium, chloride, calcium, magnesium, phosphate
Serum creatinine	
Blood urea nitrogen	
Complete blood count with differential	Hgb, RBC, HCT, MCV, MCHC, RDW WBC (total, neutrophils, lymphocytes, monocytes, eosinophils and basophils) Platelets
Arterial blood gases (ABG)	pH, $PaCO_2$, PaO_2, bicarbonate
Liver panel	ALT, AST, ALP Bilirubin Albumin
Coagulation	INR, aPTT
Glucose	
Other	Lactate, creatine kinase, troponin, C-reactive protein

aPTT activated partial thromboplastin time, *ICU* intensive care unit, *Hgb* hemoglobin, *RBC* red blood cell, *Hct* hematocrit, *MCV* mean corpuscular volume, *MCHC* mean corpuscular hemoglobin concentration, *$PaCO_2$* partial pressure of carbon dioxide, *PaO_2* partial pressure of oxygen, RDW, red blood cell distribution width, *WBC* white blood cell, *ALT* alanine transaminase, *AST* aspartate transaminase, *ALP* alkaline phosphatase, *INR* international normalized ratio

Other Investigations

In addition to patient history, the review of systems, lab and microbiology, other investigations such as diagnostic imaging and other exploratory tests could be done. Pharmacists are not required to have the skill to read the output of these tests (e.g., read a chest X-ray image); however, they need to be able to interpret the findings of these tests (e.g., written report or interaction with another healthcare team member) in the context of patient progress and medication therapy monitoring. Examples of such investigations that are helpful in the initial and follow up assessment of the critically ill include:

- Electrocardiography (ECG): An ECG records the electrical activity of the heart. It can detect arrhythmias, such as tachycardia or atrial fibrillation. In addition, QTc interval could be recorded from ECG output.
- Chest X-ray (CXR): CXR is generally ordered for intubated patients and also used to detect and monitor conditions such as pneumonia, pulmonary edema, and pneumothorax.
- Computed tomography (CT): CT scan can be used to image numerous parts of the body and can detect, for example, structural abnormalities or hemorrhages.
- Echocardiogram (ECHO): ECHO is often used to monitor heart function, such as calculating a patient's ejection fraction.

Knowledge of the results of these tests can help the pharmacist understand the patient's HPI, the course of the patient's illness, and can inform drug-related decisions, recommendations, and monitoring.

Drug Interactions

Patients in the ICU are at an increased risk for drug interactions. Rates of drug-drug interactions have been reported to be twice as high in ICU patients compared to the general hospital population [1]. The increased risk is attributed to polypharmacy and altered drugs' pharmacokinetics in the critically ill. Drug interactions are associated with longer ICU stays and can potentially have a negative impact on patients' outcomes. The pharmacist should always assess patients' medications for potential drug interactions in every practice setting, but extra diligence should be exhibited in critical care setting due to the increased risk.

Intravenous Compatibility

It is not uncommon for critically ill patients to have IV lines (peripheral and/or central). IV lines are utilized for the administration of fluids, drugs, and blood products. IV therapy offers a rapid method for delivering fluids to correct for dehydration and electrolyte imbalances. Drugs delivered through the intravenous route can have a more rapid therapeutic effect, have a complete bioavailability, and it provides an alternative

method for delivering drugs when patients have no gastrointestinal access. There are occasions that multiple IV medications and fluids are, administered through a single IV line at the same time using a y-site. A y-site is a device that has two separate tubes that can both be used to deliver fluid through and they both connect to the primary IV line; therefore, there is an intermingling of fluids in the primary IV tubing. The pharmacist has a role in assuring that drugs and fluids that are administered simultaneously at a y-site are compatible. Incompatibility can also be dependent on the concentration of each drug, the diluent solution, and the material of the drug delivery device.

There are three types of incompatibilities: physical, chemical, and therapeutic. However, note that often physical or chemical incompatibilities can lead to therapeutic changes as well. Physical incompatibility is when two or more substances are combined, and a physical change occurs, such as a change in color and viscosity, or a precipitate is formed. Chemical incompatibility is a result of chemical interactions, such as decomposition or oxidation-reduction reactions which lead to a change in the chemical properties of either substance. Therapeutic incompatibility refers to drug interactions. Implications of IV incompatibility include a potential for particulate emboli from precipitation or separation, patient harm due to toxicity, pH changes causing tissue irritation, or therapeutic failure. If there is an incompatibility, the pharmacist may recommend, for example, an alternative drug, a dosage change, a change in the solvent, or a separation of administration time. There are many resources that the pharmacist can use as a reference. References include Micromedex (https://www.micromedexsolutions.com/home/dispatch/ssl/true) and Lexicomp (http://online.lexi.com/lco/action/home?siteid=1) which includes Trissel's IV Compatibility [10]. More references on IV compatibility are available, and the pharmacist can choose a reference based on preference and availability.

Routes of Administration: Clinical Pearls

Critically ill patients may have dysphagia, have a feeding tube inserted, or have lack of gastrointestinal access. Pharmacists need to make sure that drugs are administered appropriately in ICU; the right drug in the right formulation and through the right route of administration.

- The most straightforward scenario is when the patient is able to receive oral medications. However, even if the patient can receive oral medications, it is important to look at the speech-language pathologist's report, if available, as there may be restrictions on receiving solids (e.g., tablets) vs. liquids.
- Some drugs have dosage regimen conversions among formulations (dose and/or frequency), and this should be accounted for. Examples of drugs that require dose conversions include carbamazepine and lithium. In addition, there are few drugs that are not interchangeable between the tablet/capsule and liquid form such as posaconazole.
- It becomes more difficult if the patient has a feeding tube inserted as the patient is not able to swallow any medications. In this case, the first step is to assess if tablets can be crushed and capsules can be opened or if the drug is available in an alternative liquid formulation.
- Generally sustained release (e.g., SR, ER, XL) and enteric coated tablets should not be crushed. If the XL drug also has an immediate release (IR) option available, the drug could be switched to IR and administered more frequently. Note that this is not an option for some drugs and each drug needs to be assessed individually based on its properties. For example, patients on nifedipine XL cannot be switched to the immediate release formulation due to the adverse effect profile of the latter. An alternative antihypertensive agent should be considered, e.g., amlodipine.
- The capsule may contain powder if it is an immediate release formulation or beads if it is

an extended release formulation. It is important to note that the administration of the suspended contents of the capsule through the feeding tube might not be possible in all scenarios and pharmacist should consult the pertinent product monograph for drug-specific details. For example, administering dabigatran without the capsule shell can increase the oral bioavailability from the normal range of 3% to 7% up to 75% [11]. This increase in bioavailability can put the patient at risk of adverse effects and a toxic concentration of the drug in the body; therefore, dabigatran should only be administered to patients who can take the capsule orally.

- Administration of the sustained release beads of some drugs through the feeding tube could result in tube clogging as in the cases of venlafaxine and duloxetine.
- Drugs available in film-coated formulations are generally recommended not be crushed by the manufacturer. There are multiple reasons for film coating such as masking bitter taste, light and humidity protection, ease for swallowing. Some of these reasons might not be relevant in tube-fed patients and crushing film-coated tablets is possible. For example, a patient with a feeding tube will not taste the drug and bitter tasting film-coated tablets could be crushed.
- Another option for patients with feeding tubes is to switch them to the liquid, injectable, transdermal, or rectal forms of the drug, if available, and account for any dose conversions. If switching to a liquid format, elixirs and suspensions are preferred over syrups as syrups can cause clumping in the tube. An example of a drug that cannot be given in its liquid form to a patient with a feeding tube is ciprofloxacin liquid as it will adhere to the tube and block it.
- Drugs administered through enteral feeding tubes might bind to feeds and this might result in reduced bioavailability. Holding tube feeds before and after dosage administration is recommended. Phenytoin is an example of drugs affected by this type of interaction.

There are references available that can be used as a resource to determine if a drug can be crushed, opened, etc. A reference for use of drugs in patients with a feeding tube is: *Handbook of Drug Administration Via Enteral Feeding Tubes* [12]. More references on routes of administration are available and the pharmacist can choose a reference based on preference and availability.

Altered Pharmacokinetics in Critical Illness

Pharmacokinetics of drugs are often based on studies done on healthy volunteers or based on population parameters. When a patient has an acute critical illness, multiple physiological changes take place due to the illness itself and multiple pharmacological and other supportive therapies required to treat the patient. Those physiological changes make this population different from healthy volunteers and the pharmacokinetics of drugs can be altered. Altered pharmacokinetics can lead to therapy failure, increase in adverse drug reaction, and longer hospital stay, leading to increased overall healthcare cost.

Common manifestations of critical illness which has an impact on drug pharmacokinetics include systemic inflammatory response, alteration in body fluid volume, hemodynamic instability, plasma pH changes, organ dysfunction, and shock-related redirection of the blood flow to the core organs. In critically ill patients, bioavailability of drugs from peripheral routes can be altered. Redirection of blood flow to core organs leads to reduced absorption from subcutaneous, intramuscular, and transdermal routes. Enteral drug bioavailability is also altered due to reduction in mesenteric perfusion, delayed gastric emptying, changes in gastric pH, and alteration in GI transporters. Drug distribution is also altered due to increased fluid volume, inflammation related alteration in plasma proteins, and tissue perfusion. Furthermore, drug metabolism might also be affected secondary to changes in blood flow to liver and the alteration in liver enzymes. Lastly,

excretion of drugs is also affected based on pre-existing renal dysfunction, altered blood flow to kidneys, alteration in urinary pH, augmented renal clearance (ARC), and changes in drug transporters. Also, it is not uncommon for ICU patients to be on dialysis, further complicating drugs pharmacokinetics (discussed below). Pharmacists need to be aware of the potential changes in pharmacokinetic properties that can be encountered in critically ill patients and ensure that the drugs will still be effective and safe in these patients.

Renal Replacement Therapy

AKI is more often observed in critically ill patients than the general hospital population and is a predictor of mortality [13]. Causes of AKI in the ICU population can be attributed to multiple causes such as the use of nephrotoxic medications, contrast media, and renal hypoperfusion secondary to shock, such as in sepsis or trauma.

Some patients with AKI will require renal replacement therapy (RRT) if they are at risk of or developed volume overload or a significant solute imbalance or toxicity. This is in addition to those with other indications for RRT and those with end stage renal disease (ESRD) admitted to the ICU. The following are the common indications for RRT in the critically ill [14]:

- Diuretic-resistant pulmonary edema
- Refractory hyperkalemia (>6 mmol/L)
- Refractory metabolic acidosis
- Uremic complications – pericarditis, encephalopathy, bleeding
- Rising plasma concentrations of urea or creatinine
- Oliguria (<0.5 ml/kg/h)
- Dialyzable intoxications

There are three different types of RRT that are used in the ICU: peritoneal dialysis (PD), intermittent hemodialysis (IHD), and continuous renal replacement therapy (CRRT) [14]. This is in addition to hybrid modes of RRT such as sustained low efficiency dialysis (SLED).

Peritoneal dialysis (PD) uses a dialysate to absorb waste and fluid with use of the peritoneum as a natural filter. This type of dialysis is not commonly used in the ICU and generally provides minimal drug removal.

Hemodialysis uses a dialysis machine with artificial membrane filters that utilize a concentration gradient between patient's blood and the dialysate to remove waste and fluid. IHD is provided in short intervals usually every day or every 2–3 days and can result in rapid clearance of drugs.

CRRT is a slow and continuous RRT modality that is used for critically ill patients who require RRT and are hemodynamically unstable. Depending on the mechanism of solute removal, CRRT is divided into three main types: continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF).

CRRT removes wastes at a much slower and steadier rate then IHD (Fig. 26.1).

Drug removal by RRT depends on the drug characteristics and the RRT modality. Drug-specific characteristics include molecular

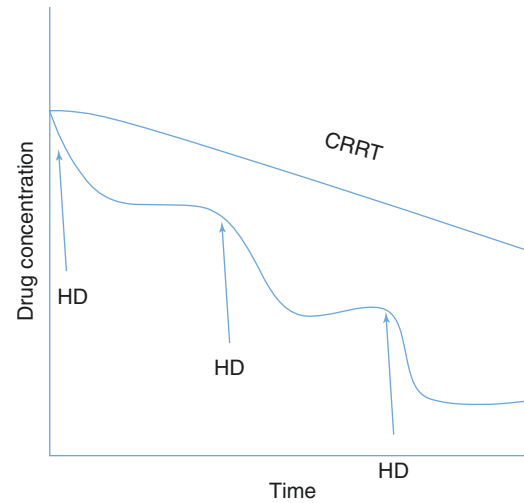


Fig. 26.1 CRRT results in continuous slow removal of solutes. IHD results in rapid and efficient removal of solutes in a short period of time and the drug clearance in-between runs depends on the patient's residual clearance. CRRT continuous renal replacement therapy, HD intermittent hemodialysis

weight, protein binding, volume of distribution, and route of drug elimination [15, 16]. Drugs with a higher molecular weight and drugs that are highly protein bound are less likely to be removed. Drugs with a smaller volume of distribution will have greater dialyzability because they have a higher concentration in the plasma compared to drugs with high volumes of distribution. The volume of distribution of a drug has less impact on drug removal with CRRT compared to IHD because of the relatively slow and continuous process of CRRT allowing drugs to equilibrate continuously with the vascular compartments. Pharmacists should also consider certain RRT factors, such as the dialysis membrane composition and pore size, the dialysate flow rate, and blood flow rates. This is in addition to the efficiency of the RRT mode on solute removal.

There are several drug dosing strategies in patients on RRT. The following are examples;

- In patients on PD, renally dose adjust based on the patient's residual renal function.
- In patients on IHD, give the dose or a supplemental dose of the drug after the HD run.
- In patients on CRRT, it depends on the patient's residual renal clearance and nonrenal clearance. This is in addition to the factors described above. For example, if a drug is 100% renally eliminated and not protein bound, dose it similar to patients with creatinine clearance of 20–30 ml/min (CRRT clearance) assuming no residual renal function. For drugs that are highly protein bound and mainly hepatically metabolized, no dosage adjustment is needed assuming no protein binding alterations.

There are references available to help pharmacists with drug dosage adjustments in patients with decreased renal function or on dialysis. Some resources available include *Seyffart's Directory of Drug Dosage in Kidney Disease* and *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults written by George Aronoff*.

Augmented Renal Clearance

Although more attention is given to adjusting the doses of renally eliminated drugs in patients with renal impairment, little attention is given if patients exhibit an augmented renal clearance (ARC). ARC is the phenomenon of enhanced renal function in critically ill patients. It is defined as a CrCl of greater than 130 ml/min/1.73m^2. This phenomenon tends to occur in the following populations: age <50 years old, patients with a history of recent trauma, male sex, and those with lower critical illness severity scores [17]. ARC has a significant impact on dosing of renally eliminated drugs such as β-lactam antimicrobials and vancomycin. ARC might result in subtherapeutic concentrations of these drugs with subsequent therapy failure and possible worsened patient outcomes. The pathophysiology of ARC is largely unknown, but it is thought to be closely related to the vigorous sympathetic response attendant with severe critical illness, increased levels of acute phase proteins, alterations in vascular tone, cardiac output, and major organs blood flow, resulting in a hyperdynamic state and augmented glomerular filtration rate. This is in addition to the effects of administration of the pharmacotherapeutic strategies aimed at improving or maintaining organ perfusion (e.g., fluid resuscitation, vasopressors) [17]. Pharmacists need to be aware of ARC and monitor patients' renal function throughout their ICU stay. If ARC is detected, pharmacists must assess patient's medications for the presence of renally eliminated drugs and assess the need for dosage adjustment and/or medication changes. Figure 26.2 provides a stepwise process for assessing an ICU patient exhibiting ARC.

Acid-Base Balance

Acid-base disorders are common complications in the ICU. Critical care pharmacists should be aware of these disorders and able to assess ABG findings and identify potential drug-related causes.

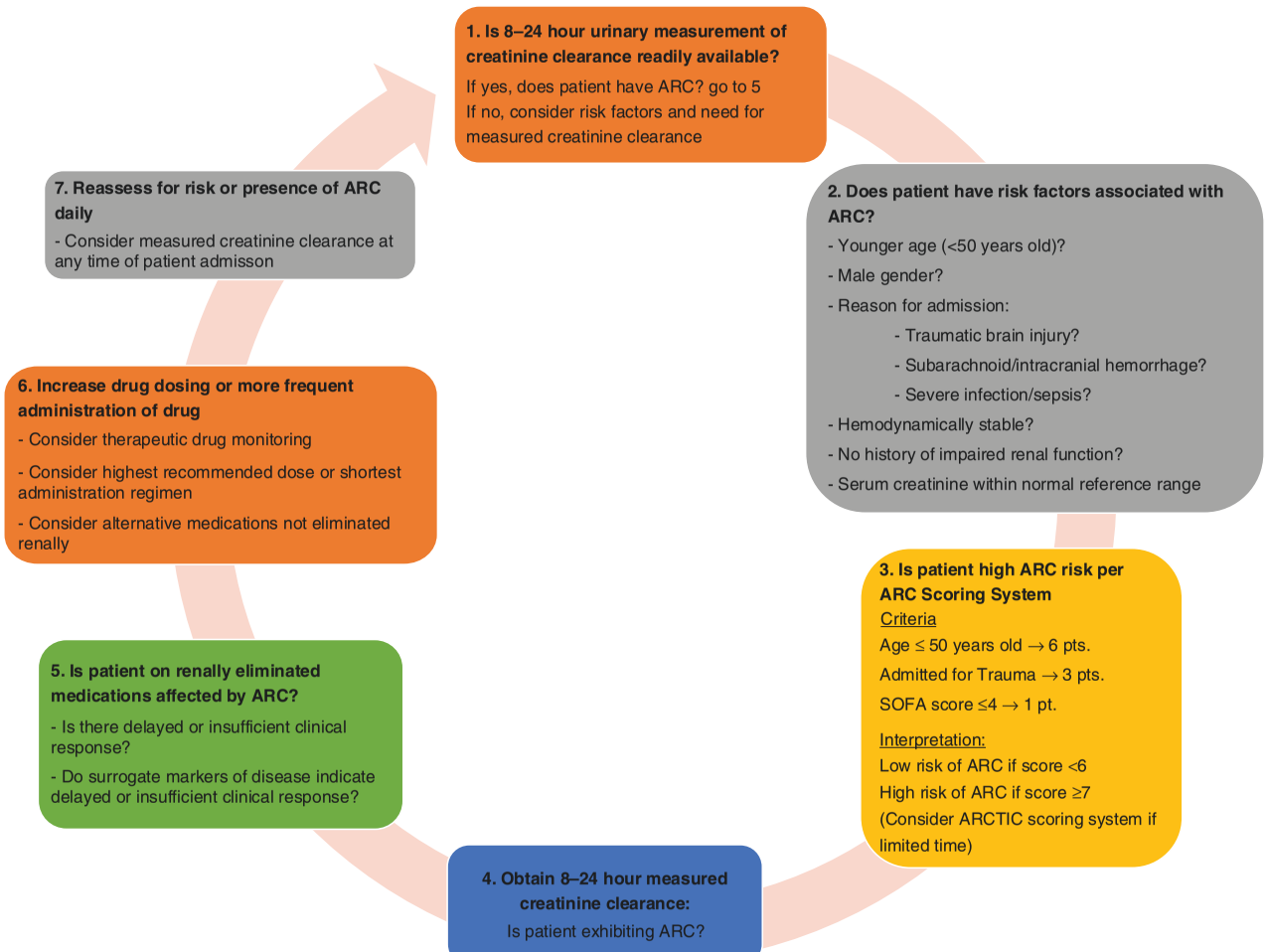


Fig. 26.2 Assessment of ICU patients for augmented renal clearance. (Reprinted from Mahmoud and Shen [17]). This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (CC BY 4.0). SOFA sequential organ failure assessment, ARCTIC Augmented Renal Clearance in Trauma Intensive Care

Acid levels are determined by the concentration of H^+ ion in the body and its concentration is tightly regulated within a normal pH range of 7.34–7.42 [18]. Acid in the body comes primarily from carbon dioxide (CO_2) as carbonic acid (H_2CO_3), which is balanced through the following equilibrium equation:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \quad (26.2)$$

This equation can be used to help explain the few mechanisms the body uses to control the level of acid in the body. There are three main mechanisms the body uses to maintain a normal body pH:

- The respiratory system controls the $PaCO_2$ and this regulates alveolar ventilation. The higher the level of H+, the more CO_2 is expired from the lungs, which decreases the concentration of acid in the body. This is a fast-acting mechanism of control.
- The renal system controls the level of HCO_3^- in the body and also can excrete other metabolic acids that the body produces, such as lactic acid, fatty acids, and ketone bodies. This is a slow mechanism of control and can take hours to days.
- Acute changes in pH can also be normalized through an acid buffer system with the use of HCO_3^-, sulfate (SO_4^{2-}), and hemoglobin.

In the healthy population, these mechanisms can control the pH and maintain it within the normal range. However, in patients with organ dysfunction and fluid imbalance, these mechanisms can fail or not be sufficient to correct for changes in balance. These patients can develop *acidemia*, blood pH is <7.34, or *alkalemia*, the blood pH is >7.42 [19]. The development of acidemia occurs through the process known as *acidosis* and alkalemia through *alkalosis*. When conducting an acid-base assessment, the first step is to determine the pH of the blood to detect the presence of acidemia or alkalemia. Next, the concentration of HCO_3^- and the pCO_2 should be measured as this can help determine if the cause of the abnormal pH is due to respiratory or metabolic processes.

There are four possible clinical manifestations of an acid-base disorder and they include respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis.

Respiratory acidosis occurs when there is an increase in the partial pressure of carbon dioxide (pCO_2) above the normal range and is defined as a pH <7.4 and pCO_2 of >40 mmHg [19]. The increase in pCO_2 is a sign that there is insufficient alveolar ventilation, and this can be caused by drug intoxication, CNS dysfunction, or respiratory obstruction or failure, such as with pneumonia, pulmonary edema, or chronic obstructive pulmonary disease (COPD). The signs and symptoms include headache, anxiety, tachycardia, hypotension, and arrhythmias and, if severe, can lead to coma. Acutely the physiological compensation for respiratory acidosis is use of the buffer system. The slower acting renal system is the main compensatory mechanism for respiratory acidosis and increases the pH by excreting H^+ and retaining HCO_3^-, which can cause metabolic alkalosis. Treatment of respiratory acidosis includes identifying and treating the cause and continued monitoring of ABGs and respiratory rate.

Respiratory alkalosis occurs when there is a decrease in the pCO_2 below the normal value and is defined as a pH >7.4 and a pCO_2 <40 mmHg [19]. The main cause of respiratory acidosis is hyperventilation; therefore, decreasing the pCO_2. Causes of hyperventilation can include hypoxia or respiratory pathology, and examining the PaO_2 can help with determining the underlying cause. Other causes of hyperventilation are CNS dysfunction, infection, drug-induced (e.g., nicotine), anxiety, pain, or can be due to overventilation that can occur in the ICU. Signs and symptoms are usually mild such as dizziness, paresthesia, and confusion but can become severe and lead to complications such as seizures. The body uses the buffer system to help compensate for alkalosis and the renal system will retain H^+ and excrete HCO_3^- to lower the pH, which can cause metabolic acidosis. The treatment is similar to acidosis with trying to identify and treat the cause and continuing to monitor ABGs and respiratory rate.

Metabolic acidosis occurs when there is a decrease in HCO_3^- and is defined as a pH <7.4 and HCO_3^- <22 mmol/L [19]. Signs and symptoms of metabolic acidosis include hyperventilation, hyperkalemia, insulin resistance, nausea and vomiting, and CNS effects such as confusion and coma. The respiratory system compensates for the low pH by decreasing the pCO_2 in the body through hyperventilation, and this mechanism can lead to respiratory alkalosis. The cause of metabolic acidosis can be assisted by calculating the anion gap (AG), which is the difference in unmeasured anions and cations. The AG is calculated with the following equation and has a normal range of 8–14 mmol/L.

$$AG = [Na+] - [Cl-] - [HCO^3-] \quad (26.3)$$

If the AG is normal, the cause of the acidosis is not due to an unmeasured cation or anion, and the primary cause is a loss of HCO_3^-. Causes of normal AG acidosis can be remembered with the acronym HARDUP, which stands for hyperalimentation, acetazolamide, renal tubular acidosis, diarrhea/dilution, ureteral diversion, and pancreatic fistula [20]. If the AG is >14 mmol/L, it is due to an excess of unmeasured cations or anions, and causes can be remembered with the acronym MUDPILES [20]. MUDPILES stands for methanol/metformin, uremia, diabetic ketoacidosis, propofol/paraldehyde, iron/isoniazid, lactate/linezolid, ethylene glycol, and salicylates/starvation [20]. Finally, a decreased AG which is <8 mmol/L is uncommon and is usually associated with hypoalbuminemia [21]. Treatment of metabolic acidosis includes identifying the cause and treating it and potentially the administration of sodium bicarbonate.

Metabolic alkalosis occurs when there is an increase in HCO_3^- and is defined by a pH of >7.4 and HCO_3^- >28 mmol/L [19]. Signs and symptoms include hypoventilation, hypokalemia, confusion, muscle weakness, tachycardia, and arrhythmias. The respiratory system compensates for the high pH by increasing the pCO_2 in the body through hypoventilation and this mechanism can lead to respiratory acidosis. Causes include a loss of H^+ (e.g., from vomiting or diuretics), intake of excess alkali substances (e.g., excessive antacid use) or decreased renal function. Treatment includes identifying the cause and treating and correcting any fluid and electrolyte imbalances.

Table 26.6 Expected changes in primary acid-base abnormalities[a]

Disorder	pH	HCO_3^-	pCO_2
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑
Acute respiratory acidosis	↓↓	↔	↑↑
Chronic respiratory acidosis	↓	↓↓	↑
Acute respiratory alkalosis	↑↑	↔	↓↓
Chronic respiratory alkalosis	↑	↓↓	↓

HCO_3^- bicarbonate, *pCO_2* partial pressure of carbon dioxide

[a]Adapted from Hubble [18], Copyright 2004, with permission from Elsevier

The changes that occur with ABGs in each acid-base disorder are presented in Table 26.6. Maintaining an acid-base balance to compensate for any abnormalities and often the compensation for one disorder can lead to the development of another. For example, compensation for respiratory acidosis can lead to metabolic alkalosis. Due to the fast-acting mechanism of the respiratory system, respiratory acidosis or alkalosis reflects a current body dysfunction, while the slow-acting metabolic system could be caused by something that happened hours to days ago. The main treatment for these disorders is treating the underlying cause of the imbalance and with treatment the imbalance should correct itself.

Conclusion

Pharmacists provide an essential clinical role in an interprofessional team and contribute to patient care, safety, and positive patient and clinical outcomes. Pharmacists working in critical care are becoming the standard of care and present an opportunity for pharmacists to work in a specialized practice. Critically ill patients require daily assessments and assessments on unique topics due to the complicated nature of their illnesses. The pharmacist needs to have the knowledge and the skills to provide care for these

patients. Working in critical care can be challenging for a practitioner, but it can also be a practice site that provides learning opportunities and rewarding experiences.

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Assessment Considerations in Older Adults

27

Cheryl A. Sadowski

Chapter Objectives

1. Describe the process of comprehensive geriatric assessment.
2. Identify the domains of comprehensive geriatric assessment.
3. Describe practical tools that pharmacists can use in their assessment of older adults.

Background

Assessment of older adults, particularly those who are multimorbid, complex, or frail, requires a broader interprofessional assessment. This approach is referred to as comprehensive geriatric assessment and includes health and non-health domains. The assessment is completed with an interprofessional team, and the process focuses on functional abilities and values and goals of the patient, rather than cure or simply chronic disease management. The assessment has many domains, including cognition, function, activities of daily living, nutrition, social supports, and others. Pharmacists have an important role to play in contributing to the geriatric assessment through feedback on a variety of domains and particularly through assessment of medications.

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Definitions

Geriatrics is the health sciences specialty of caring for older adults. This specialty is sometimes referred to as a supraspecialty, versus a subspecialty, because it addresses not only the management of health conditions under internal medicine but also it includes the overall health and wellness of older adults [1, 2]. The broader study of aging and older adults, using bio-psycho-social sciences, is the study of gerontology [3].

The current terminology centres on "older adults" or "older people," rather than terminology that infers that these individuals have less value or are "senile" in old age [4]. Language is evolving in geriatrics to move away from terms that support negative stereotypes. In some clinical and research settings, terms such as young-old, middle-old, or old-old will be used to categorize the chronological age of this older age group, but this terminology is shifting to identify specific age ranges (e.g., age 65–74, 75–84, and 85 and older). The term "centenarian" refers to someone who has reached 100 years of age and "supercentenarians" as those reaching 110 years. These definitions are not just used to address demographic analyses through the national census but to consider unique needs of specific age groups, to direct healthcare services, to design and analyze research meaningfully, and to communicate correctly to and about the patients one cares for.

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Demographics

The 2016 census in Canada showed that for the first time in Canadian history, seniors outnumbered children aged 14 and under, with seniors making up 16% of the population. The segment of the population aged 65 and older increased by 20% from the previous 5 years, noted in the 2011 census [5]. This dramatic increase is due to two factors: improved life expectancy and low fertility rates. Aging and an increasing number of older adults are a global phenomenon, with the age group of 60 years and older growing faster than all younger groups [6]. United Nations reports indicate that the number of people over age 80 will triple by 2050, with similar increases expected in Canada [6, 7].

Epidemiology and Pharmacoepidemiology

Older adults represent only 16% of the Canadian population, yet they receive 55% of publicly funded drug spending [8]. Seniors use more medications than any other age group, with the average senior in Canada using seven different medication classes over a 1 year period [8]. The most common medication class used by seniors in Canada is the HMG-CoA reductase inhibitors (statins) [8]. In addition to medications, over 60% of seniors use dietary supplements (e.g., vitamins) [9].

Seniors also use the healthcare system more than other age groups, with significantly longer stays in hospital, particularly for those age 75 and older [10, 11]. The healthcare costs for seniors also increase with age, with the most significant increase at age 80, where it is estimated that each senior age 80 years and older costs approximately $21,000 (CDN) per year in 2013 [12].

Disease and disability also increase with age. The most common single "diagnosis" is multimorbidity, as 75% of seniors have co-existing conditions [13]. Another unique aspect of geriatric care is the concept of the "geriatric syndrome," which is a multifactorial condition involving age-related risks and stressors that together overwhelm the patient's system [14]. Syndromes are challenging to address due to their multifactorial nature, but there are resources to assess and manage common syndromes, such as falls or urinary incontinence.

Impact of Aging

At a macro level, an aging world affects resources and healthcare planning, in addition to public policy and health promotion in every country. Within the context of individualized patient care, it is important to consider the physiologic changes that occur with aging. These changes are part of normal aging and are not pathological (Table 27.1) [15]. These changes can subsequently affect pharmacokinetic parameters, with the least impact on drug absorption (Table 27.2) [16, 17]. Furthermore, changes in receptor density and affinity, post-receptor changes, or negative feedback can all lead to a change in how older adults respond to medications, which is described under "pharmacodynamics" [17–19]. In most cases, older adults are more sensitive to medications, and adverse events may occur (Table 27.3).

There are changes in how older adults present with illness. Often, seniors have vague complaints or do not follow the "textbook presentation" of a disease. This can be due to

Table 27.1 Physiologic changes due to aging

Body system	Key changes
Body composition	↑ Fat ↓ Lean
Cardiovascular system	↓ Beta receptors ↓ Cardiac output
Pulmonary system	↓ Cilia ↓ Vital capacity ↓ Maximal breathing capacity ↑ Residual volume
Gastrointestinal system	↑ Gastric pH ↑ Gastric emptying time
Hepatic system	↓ Size ↓ Splanchnic blood flow
Renal system	↓ GFR ↓ Nephrons
Endocrine system	↓ Hormonal secretions
Nervous system	↓ Blood flow to CNS

CNS central nervous system, *GFR* glomerular filtration rate

multimorbidity, with co-existing conditions affecting how another disease presents or progresses, or may be due to a physiologic decline with aging that affects the acuity and type of symptoms experienced [20, 21].

The Imperative

There is a demographic imperative to address the care gap within the healthcare system by better preparing professionals to assess and manage care for older adults. Given the unique presentation of older adults, changes in pharmacokinetics and pharmacodynamics, and complexity in presentation, pharmacists require a deeper understanding of the interprofessional and comprehensive assessment processes required. The unique role of the pharmacist is essential in contributing to comprehensive geriatric assessment. The purpose of this chapter is to provide an introduction to the assessment of older adults for the pharmacist.

Table 27.2 Changes in pharmacokinetic parameters due to aging

Parameter	Change
Absorption	Minimal change in GI absorption of passively absorbed medications; slight decrease in actively absorbed medications (e.g. B12, iron) IM absorption may be affected by blood flow (e.g., bedridden patients)
Distribution	Increased distribution of lipid-soluble medications, leading to longer half-life Decreased distribution of water-soluble medication, leading to higher maximum serum concentration C_{Max}
Metabolism	Slower first-pass effect Slower phase I metabolism (oxidation/reduction) Minimal changes in phase II metabolism (conjugation)
Excretion	Decreased renal elimination

GI gastrointestinal, *IM* intramuscular

Comprehensive Geriatric Assessment

The use of comprehensive geriatric assessment (CGA) recognizes that a disease-based model for assessment and care does not work well for older adults who have multiple comorbidities in addition to complexities of aging, such as the lack of caregiver support, financial concerns, or difficulty navigating a fractured healthcare system. Those with multimorbidity or frailty are best suited to CGA, versus implementing this process for all individuals age 65 years and older [22]. The difference in CGA from regular patient assessment is that it includes non-health domains, focusing on functional capacity and quality of life and including an interprofessional team [23]. The core team is usually made up of a physician, nurse, and social worker, and additional assess-

Table 27.3 Examples of pharmacodynamic alterations due to aging

System or function affected	Proposed mechanisms	Medication examples
Postural control	Fewer dopamine D2 receptors in striatum	Antipsychotics
Orthostasis	Blunting of β receptors response, receptor downregulation, changes in vascular tree and autonomic nervous system	Blood pressure medications, TCAs, antipsychotics, diuretics
Thermoregulation	Poor temperature-regulating mechanisms (e.g., shivering, ↓ metabolic rate, ↓ vasoconstriction, ↓ thirst response, ↓ awareness of environmental or body changes in T, unable to tolerate extremes in temperature)	Medications affecting awareness, mobility, muscular activity, vasoconstrictor mechanisms CNS meds (e.g., phenothiazines, barbiturates, benzodiazepines, opioids, ethanol)
Higher cognitive function	Neuronal loss, receptor downregulation	Central anticholinergics, stimulants
Anticoagulation	Poor hepatic production of coagulation factors, dietary intake	Anticoagulants, thrombolytics
Tardive dyskinesia	Impaired or decreased dopamine-synthesizing neurons	Antipsychotics
Arrhythmias	Cardiac hypersensitivity	Antiarrhythmic medication

ment is provided by physiotherapists, occupational therapists, spiritual care professionals, psychologists, and, notably, pharmacists [24]. The process requires collaboration, but this may take place within the same setting, around the same time, or virtually and sequentially [24]. The role of the pharmacist primarily focuses on medication review, but an understanding of the other domains of assessment is essential to integrate appropriate interventions. Pharmacists may also have the training to become proficient at other tests in other domains, which may augment the efficiency of the care team [25].

CGA is defined as "a multi-dimensional multidisciplinary diagnostic process focused on assessing an older person's medical, psychological, and functional capability in order to develop a coordinated and integrated plan for treatment and long-term follow-up focused on the individual's needs" [22]. The initial assessment includes a comprehensive care plan, goals identification and who is responsible for each one, and a timeline to review progress. The CGA process originated in hospital and demonstrated that older adults who underwent CGA, compared to usual hospital care, had less risk of being institutionalized, dying, or having a functional decline [26, 27].

Currently there is no standardized set of tools, but the content below includes the most common resources for validated assessments under each domain. Table 27.4 depicts general CGA domains.

Table 27.4 Domains of comprehensive geriatric assessment

Domain	Example
Mental status	Psychosis, depression, anxiety
Cognitive status	Cognition, memory
Social status	Social supports Availability of spouse, family, friends
Values	Decisions regarding DNR, living will, power of attorney
Spirituality	Supports, beliefs Activity and socialization
Economic status	Ability to pay for care or treatments
Physical status	Review of disease states Review of medications
Functional status	Ability to do activities of daily living
Senses	Hearing, vision
Health maintenance/ disease prevention	Primary, secondary, tertiary prevention Geriatric syndromes, falls, incontinence Nutrition
Risks	Abuse

DNR do not resuscitate

Interprofessional Assessment of Health

The pharmacist's expertise in medications supports the primary role focusing on medication assessment. However, the pharmacist can participate in other components of CGA, learning to use the tools in a validated manner or in terms of interpreting the findings of the other team members in order to apply that learning to decisions about medications.

Physical Assessment

Pharmacists are familiar with vital signs and the routine measurement of pulse and blood pressure. The standard for a physical examination applies to older adults, but a few adjustments to focus on issues that are more prevalent in seniors [23]. One area that a pharmacist can measure is orthostatic blood pressure drop, which requires a sitting or supine blood pressure, followed by a repeated blood pressure measurement after the patient stands. Prevention of disease should also be assessed, such as inquiring about vaccination status.

Mental Health

Cognitive impairment and dementia occur almost exclusively in geriatrics. An assessment for cognitive functioning is a core component of CGA. The most common starting point is a screening test, such as the *Mini-Mental Status Exam* (MMSE), which provides some information about the patient's cognitive abilities but is not diagnostic for dementia [28]. Another tool that has gained popularity for a more specific assessment of exec-

utive function is the *Montreal Cognitive Assessment* (MoCA) [29]. Both of these tools are relatively brief, about 5–10 minutes, have a series of healthcare professional scored questions, and result in a score out of 30 points. There are cut-points for normal versus abnormal, which can assist clinicians in identifying if further assessments are required. For example, a 26/30 or higher would be considered normal, but lower scores should be investigated further, for possible disease or medication cause of impairment. *The clock drawing test* is a relatively quick test to administer, by observing the patient draw a clock, but it has a variety of proposed scoring methods [30]. *The 2 trail making tests*, assess sequencing, prioritization, visuospatial skills, and handling multiple cognitive tasks. The first trail making test, includes sequential numbers or letters (A,B,C; 1,2,3), and the second includes alternating numbers and letters (A,1,B,2,C,3) [31]. In-depth cognitive assessments are conducted by occupational therapy or a neuropsychologist who can target specific domains with focused validated tests [32]. The pharmacist can administer some of these tests but should be cautioned that findings of low performance may be challenging to discuss with patients and also create a situation where further investigations and interventions should be addressed that may be beyond the scope of the practice of a pharmacist (e.g., driving ability, living independently).

The assessment of mood is also part of a geriatric assessment. A screening tool that is commonly used is the *Geriatric Depression Scale Short Form* (GDS-SF) which has 15 questions, scored as yes/no by the patient [33, 34]. It is important to use a geriatric-focused questionnaire, as depression screening tools for younger patients often include questions about family demands or work, which may not be relevant for someone who is retired or who is not living with children. There is also a concern that patients with dementia will require an adapted tool that does not directly ask them questions that require abstract thinking. *The Cornell Scale* for Depression is such an instrument, which has the clinician interact with the patient and then the clinician fills out a scale regarding observations about the patient, such as behaviours or physical signs [35]. This type of observation takes more time than a straightforward questionnaire but is appropriate for a patient with dementia.

Function

A functional assessment is generally in the domain of rehabilitation therapists, but the pharmacist should be able to understand the impairment based on the assessments and scores. The two broad areas are the (basic) activities of daily living (ADL), or the self-care activities such as toileting, eating, and dressing, and the instrumental activities of daily living (IADL), which are activities needed to live independently, including taking medications, housework, and preparing meals. The best approach to assessing ADL and IADL is to observe the patient, which can be done in a simulated laboratory setting or in the patient's own home during a home visit. There are formal measures for ADL assessment, led by the *Katz Index of Independence in Activities of Daily Living*, which asks or observes about independence in six areas and scores the patient as independent (score of 1) or dependent (score of 0) [36]. The IADL first-line tool is the *Lawton-Brody*, which also scores patients as 0 or 1 on their ability to perform eight different tasks [37]. There are a variety of other measures that a physiotherapist may use to assess function and disability, such as the *Functional Independence Measure* (FIM) which can also be combined with the *Functional Assessment Measure* (FAM), which scores the patient from 1 (total assistance) to 7 (fully independent) in six different domains, including cognition, communication, and sphincter control [38]. Pharmacists should particularly take note of functional measures, which can determine if the patient can independently take his/her medications or safely manage self-care activities.

Geriatric Syndromes

Geriatric syndromes are challenging to address because they are multifactorial and involve mul-

tiple organ systems [14]. Syndromes do not follow a disease trajectory, but they are associated with functional decline and disability [14].

Frailty

Frailty is a concept that is still being debated in terms of definition and criteria, but one method used in practice, research, and by organizations developing clinical practice guidelines is the Canadian Frailty Scale, a nine-item scale that provides assessment by image/picture, with stage 1 being fit and stage 9 being terminally ill [39].

Falls

Falls are also common in older adults, leading to fractures, soft tissue injuries, and decreased socialization through a fear of falling [40]. Inquiring about falls can be done by a variety of health professionals, including pharmacists who work in the community [41]. Pharmacists can ask the patient if he/she has fallen in the past month, 6 months, or the previous year and if the fall was associated with any injury. Falls are multifactorial and can include environmental, behavioural, medical, and medication risks. Determining if the patient is at risk for medication-related falls is a priority for pharmacists. The medications with the strongest association for falls are psychotropics, including sedative hypnotics, antidepressants, and antipsychotics. These medications can increase the risk of falls by 50% from the baseline [42, 43]. Other medications that can contribute to the fall risk include opioids and diuretics, although the risk is less than psychotropics and may decrease over time (Table 27.5) [44–47]. Pharmacists can assess risk for falls through a medication review and also conduct simple observations, or even validated measures, in the community pharmacy. Some examples that may be used by a physiotherapist include the *Tinetti Balance and Gait Examination*, a series of assessments on gait and balance, scored from 0 to 2 [48]. A simple assessment is the *Timed Up and Go* (TUG), which requires the patient to be seated, rising from that position without using his/her arms, walking 3 m, turning around, and sitting again. The test is timed and the patient should not take longer than 16 seconds [49]. Another simple test is the *Functional Reach Test*, where the patient stands close to a wall and reaches out his/her hands. The measurement should be at least 25 cm [50]. However, pharmacists should consider the layout and safety features of their pharmacy before administering this test, as a patient who is at risk of falls could fall and injure him/herself during the activity. Concerns about geriatric patients who have gait or balance problems can be referred to a physiotherapist for further workup and in-depth assessments.

Lower Urinary Tract Symptoms

Older adults are more likely to experience lower urinary tract symptoms (LUTS) and urinary incontinence (UI). One tool to start the conversation and screen both males and females is the *International Consultation on Incontinence Questionnaire* (ICIQ), which includes four ques-

Table 27.5 Medications associated with fall risk

Medication class	Example	Risk
Sedative hypnotics	Lorazepam, diazepam, zopiclone	High[a] OR = 1.3–1.6
Antidepressants (TCA, SSRI)	Amitriptyline, sertraline, citalopram	High[a] OR = 1.5–1.6
Antipsychotics	Quetiapine, haloperidol	High[a] OR = 1.3–1.7
Diuretics	Hydrochlorothiazide, furosemide	Moderate OR = 1.1
Opioids	Morphine, hydromorphone	Low[b] OR = NS–1.3
NSAIDs	Ibuprofen, naproxen	Low[b] OR = NS

OR odds ratio, *SSRI* serotonin selective reuptake inhibitors, *TCA* tricyclic antidepressants
[a]Studies consistently found to be statistically significant
[b]Studies inconsistent in statistical significance

tions, starting with, "How often do you leak urine?" [51]. *The Bladder Self-Assessment Questionnaire* (B-SAQ) includes four questions similar to the ICIQ but also asks the patient to score how much of a bother those symptoms are [52]. There are also questionnaires specific to the type of LUTS, such as a *benign prostatic hyperplasia (BPH) questionnaire* for men, with seven questions on symptoms and four questions on bother, and an eight-question *overactive bladder questionnaire (OAB-V8)* for both men and women [53, 54]. After compiling the scores, the pharmacist can discuss concerns about LUTS or, in some cases, encourage the patient to see the family physician for further investigation and more invasive examinations (e.g., pelvic and/or rectal exam).

Nutrition

Assessing nutrition in older adults is important to prevent frailty and cachexia. There are often changes with dentition and socialization affecting eating patterns and functional abilities and resources to purchase and prepare healthy meals. Asking a question about their ability to swallow can inform about nutritional concerns, as well as swallowing of medications, which can be done with the *EAT-10*, a ten-item questionnaire, scoring people from 0 (no problem) to 4 (severe problem) [55]. The *mini-nutrition assessment (MNA)* is commonly used in seniors, with scoring for food intake, weight loss, mobility, stress, neuropsychological problems, and body measurements [56].

Values

To determine a patient's priorities, a model of the 5Ms is supported by both the American and Canadian Geriatrics Societies [57]. This centers around asking a question, such as "What *m*atters most to you?" The other Ms. include *m*emory/*m*ind, *m*obility, *m*edications, and *m*ulticomplexity. This can help the clinician direct the assessment to delve deeper into some areas or provide guidance on the types of interventions that can be recommended.

Sensory Impairment

Senses are extremely important to assess as older adults experience changes in taste, vision, and hearing. In older adults, the loss of vision and hearing has dramatic effects on function and quality of life, and impaired taste can lead seniors to add excessive amounts of salt to food. Vision can be assessed by using a *Snellen chart* and *eye chart* that measures visual acuity. Referral to an ophthalmologist for screening for diseases, such as glaucoma, could be considered [58].

Hearing is most effectively done through observation, such as noting when patients have difficulty in conversation or exhibit behaviours such as looking to a partner for support. One recommendation is to simply ask the patient and caregiver/partner/family member if the patient is having difficulty hearing. Other recommended screening approaches include a *whisper test*, where a series of digits or letters are read aloud in a whisper, about 1 m behind the patient, and he/she repeats what is heard [59]. A validated questionnaire is the *Hearing Handicap Inventory*, which includes 25 questions that are scored out of 100 [60].

Social Supports

In order to provide appropriate recommendations for seniors, it is important to understand their circumstances and any potential harm they might be at risk of. Usually, these areas are assessed by a social worker, nurse, or medical trainee using a checklist of questions. These questions include if the patient is living with someone, what supports the family, friends, or caregivers provide, if there are formal or informal caregivers involved, the type of housing he/she is residing in, the social network, environmental safety, or indicators of abuse [23]. Focused questions can also include the amount of financial resources the patient has available, how much informal or formal care is costing, or government funding accessed.

Another area of support that patients might describe is spiritual support. Religion and spirituality may play a role in determining choices related to medications (e.g., the use of animal or

pork by-products), expectations for family, decisions about care, or the type of institutional supports the patient will accept. It is therefore necessary to ask about religion, spiritual beliefs, and the social, emotional, or psychological support that can be provided [61].

Medication Assessment in Older Adults

There are a number of generic tools that pharmacists can use for medication reviews. These include programs such as MedsCheck or other local tools. However, most of these tools are not designed for the unique multimorbid, complex, or frail older adult. Pharmacists should consider using tools that have been adapted or validated for seniors, including *TIMER* (Tool to Improve Medications in Elderly via Review), *NO TEARS, DITTO* (Drug Importance Tool for Treatment Optimization), the *Hierarchy of Utility*, or a ten-question self-administered tool that identifies medication risk in seniors (Table 27.6) [62–66]. These tools may improve the efficiency in identifying drug-related problems in seniors by providing a guiding framework and questions to ask, in the context of multimorbidity, grey areas of decision-making and the potential for a high number of medications. The tools do not provide a score or direction that indicates an intervention is necessary, but they provide information for the pharmacist to consider in identifying polypharmacy, undertreatment, adherence, or management concerns. There is no evidence that one tool is superior to another.

Table 27.6 General medication assessment tools for geriatrics

Tool	Design	Categories and content included
TIMER	Structured two-page questionnaire with question prompts, checkboxes, tables, and references to guide the review	Medication insurance coverage Adherence Medication safety (adverse events, drug interactions Therapeutic goals (related to disease states, common geriatric syndromes)
NO TEARS	Acronym to assist healthcare provider in reviewing each medication	Need and indication Open questions Tests and monitoring Evidence and guidelines Adverse events Risk reduction or prevention Simplification and switches
DITTO	A grid that is used once the importance and indication of medications are identified	Grid includes four levels of importance Vital, important, optional, not indicated Reasons for use include Cure, prevent complications, relieve symptoms
Hierarchy of utility	A sequence of ten steps to determine potentially inappropriate medications (PIM); six questions to determine the strength of indication; eight questions regarding the potential misuse or safety concerns	Example of questions included Potentially inappropriate medication *Accurately ascertain all medications used* *Define overall goals of care* Strength of indication (step 8 in the PIM assessment) *Does medication provide immediate relief of distressing symptoms?* Potential misuse *Is the medication associated with little benefit and high risk of toxicity in most older patients?*
Ten-question	A self-administered questionnaire with ten questions to be completed by the older adult	Example of questions included *Do you currently take five or more medications?* *Is it difficult for you to follow your medication regimen or do you sometimes choose not to?*

Medication Appropriateness

Medications are identified as inappropriate in seniors if they overall cause more harm than benefit, and there are safer alternatives available. There are two main types of tools—explicit and implicit, which are described below (Table 27.7) [67]. Explicit tools include the ACOVE-3 criteria, Beers criteria, STOPP/START, and others [68–71]. The *Beers criteria* is updated every 3 years by the American Geriatrics Society and includes a list of potentially inappropriate medications (e.g., first-generation antihistamines), a list of medications to avoid in particular disease states (e.g., anticholinergic medications in delirium), medications to be used with caution (e.g., SSRI, which can cause SIADH), drug interactions, and medications requiring adjustment for renal function. The *STOPP criteria* were developed in Ireland for a context of practice in the European Union. They have many overlapping criteria with the Beers criteria, such as "do not initiate tricyclic antidepressants as first line antidepressant therapy." Because these tools are written as statements without any scoring required, they can be built into software to alert the clinician when a particular potentially inappropriate medication is being dispensed or used, or the tools are available through apps on mobile devices. They are designed to be used as a guide for decision-making about prescribing, rather than mandatory criteria to follow without considering the patient in the decision-making. The *START* component of the STOPP/START criteria includes a list of medications that should be started, such as using bisphosphonates and vitamin D in a patient on long-term corticosteroids.

An implicit measure of medication appropriateness is the *Medication Appropriateness Index* (MAI) [72]. This tool is primarily used in research, due to the time it takes to administer ten questions about every medication the patient is taking. For an average regimen in seniors, it would take approximately 45 minutes to use. In addition, this tool does not identify medications that are missing. Despite these limitations, the questions are practical and can guide the pharmacist on decisions about the medications (e.g., Is the medication effective for the condition?).

Medication Administration

Medication management is challenging for many older adults due to the multistep process (e.g., ordering, obtaining, packaging/sorting, actuating, swallowing), the complexity of the regimen, and the physical and cognitive challenges of using multistep devices. Sometimes, disease can play a role, such as osteoarthritis, or visual impairment, which can affect how a senior can open blister packages, administer eye drops, or dial an insulin pen. There are tools that have been developed to identify functional challenges in administering medications [73]. These tools have been used primarily in research studies but could be used in

Table 27.7 Comparison of medication appropriateness tools

	Explicit	Implicit
Design	Criterion-based	Judgment-based
Development	Developed from published reviewers, consensus, expert opinions	Clinician uses information from the patient and published work
Clinical judgment	Applied with little or no clinical judgment	Clinician makes judgments about appropriateness
Focus	Usually drug or disease oriented	The patient
Benefit	Applied to databases Simple to apply	Most sensitive approach for the patient
Limitations	Do not take into account all factors that define high-quality healthcare for the individual	Time-consuming to provide care
	Do not address the burden of comorbid disease, patient preferences	Variable – depends on clinician's knowledge, skills, attitude
Example	Beers criteria	Medication appropriateness index

clinical practice. One drawback is that many take more than 15 minutes to administer, which can be problematic in terms of a comprehensive geriatric assessment. Some tools provide a standardized regimen to test the patient, rather than focusing on the patient's own regimen, which can make it difficult to apply the findings to make appropriate interventions for a specific patient. Two tools, the *Self-Administration of Medication* (SAM) and the *Drug Regimen Unassisted Grading Scale* (DRUGS), require less than 15 minutes to administer, assess the patient managing his/her own regimen, and identify if the patient requires additional supports, all of which may be useful to inform pharmacists and can be built into the medication review process [74, 75].

Clinical Pearls

- The comprehensive geriatric assessment is a broad assessment of health and non-health domains, which the pharmacist should be familiar with.
- The pharmacist should participate in geriatric assessment by contributing to medication assessment and engaging in dialogue about other domains with the interprofessional team.
- The pharmacist has an important role to play in assessing medications in older adults in all settings.
- There are a variety of validated tools to assess the appropriateness and functional management of medication that the pharmacist can incorporate into practice.

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28 Assessment Considerations in Pediatric Patients

Deonne Dersch-Mills

Chapter Objectives

1. Recognize challenges related to patient assessment that are unique to pediatrics and neonatology.
2. Describe the required components of a complete pharmacy assessment that are unique to pediatrics and neonatology.
3. Gain a basic understanding of the differences in pediatric assessment as it relates to vital signs and common laboratory parameters.

Background

Pediatric pharmacy technically includes the care of any patient under the age of 18 years, although practically patients over the age of 15 can usually be cared for following similar dosing/monitoring as in adults. In Canada in 2017, children under 12 years comprised ~15% of the Canadian population (Statistics Canada, Population by sex and age group 2017), and accounted for 6.4% of hospital discharges (~3% not including births in hospital) [1]. Approximately 50% of Canadian children receive one or more medications each year; this is up to 79% in infants <1 year old [2, 3]. While medication use is not uncommon, polypharmacy is much less common than in adult patients. Around 20% of US children received at least one medication in the previous week, but less than 6% had used two or more medications in the previous week [4, 5]. The most common medications filled for children in community pharmacies in 2012 included antibiotics (amoxicillin, azithromycin, and cefprozil most commonly), asthma medications (salbutamol, fluticasone, montelukast), and medications for attention deficit hyperactivity disorder (ADHD) (methylphenidate primarily) [2].

Before moving forward, it is important for pharmacists to understand age-related terminology for children. Gestational age (GA) is the duration of time a newborn has been in utero (full term is considered ~40 weeks) while post-natal age (PNA), also known as chronological age (CA), is the duration of time since birth (e.g., 2 weeks old). Corrected gestational age (CGA) or post-menstrual age (PMA) are terms used most commonly in infants born prematurely, and refer to their gestational age plus post-natal age. For instance, a baby born at 30 weeks GA, with a PNA/CA of 10 days would have a CGA/PMA of 31 weeks and 3 days (commonly abbreviated as 31 + 3 weeks). A neonate (or newborn) is an infant <28 days PNA/CA, or for premature infants, less than 44 weeks CGA/PMA. The term "infant" typically refers to a range of PNA/CA from 28 days to 1 year. The term "toddler" typically refers to age 1–3 years, and "school-age"

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refers to age from 4 to 9 years. "Adolescent" typically refers to age 10–19 years, though the true onset of adolescence is determined by the onset of puberty. These distinctions are important due to developmental changes that occur in pharmacokinetics (see more below).

There is a distinct lack of research on medication use in children, which adds its own challenges to the practice of pharmacy in children. Up to 90% of medication use in hospitalized children and 30% of medication use in ambulatory children are considered "off-label," that is, not included in the product labeling/monograph and thus not supported by the manufacturer [2]. Only 25% of medications on the market are approved for children, and this number is even less for infants [6]. This results in a lack of detailed pharmacokinetic, dosing, adverse effect, and efficacy data for appropriate medication management in children. As well, due to the lack of studied indications in children, there is little impetus for manufacturers to make formulations appropriate for children and so formulation issues related to availability, palatability, excipients, or measurability are commonplace.

Due to the abovementioned factors, children are at higher risk of medication errors and have a higher risk of harm from medication errors, so the pharmacist plays an important role in caring for infants and children who use medications [7]. Approximately 8% of pediatric Emergency Department visits are medication-related, of which 2/3 are deemed preventable (examples include adverse drug reactions, sub-therapeutic doses, or non-adherence due to a variety of factors) [8]. There are an estimated 0.85 adverse drug reactions per 100 inpatient admissions in pediatrics, of which 21% would be considered preventable [9]. Statistics like this highlight the importance of a complete pharmacist assessment for children using medications.

In many ways, assessment of a pediatric patient is not different than assessment of an adult patient. Pharmacists should gather information on medical history, medication history, medical conditions, and any other relevant information, and then ensure that all medications are indicated, dosed appropriately, effective, safe, and adhered to. However, each of these steps contains nuances for infants and children. There may be additional steps within each component of the assessment, and there is a significantly smaller evidence base to support decisions and judgment calls made within each step of the assessment.

Pharmacokinetic Differences

One of the major nuances between pediatric and adult assessments is the need to consider pharmacokinetic ontogeny, or pharmacokinetic differences based on the age of the child. While it is not surprising that there are pharmacokinetic differences between children and adults, there are also important differences between premature newborns, term newborns, infants, toddlers, school-age children, and adolescents. Table 28.1 provides a summary of major pharmacokinetic considerations in infants and children. This variability in pharmacokinetics makes dosing medications in children especially challenging as there is no "standard" dose of a medication. Medication doses may vary based on CGA, PNA, as well as body weight or surface area. Most notable is the need to use neonatal (not pediatric) dosing in newborns as the first few months of life are characterized by rapidly changing organ function (renal and hepatic most importantly) as well as changes in drugs' volume of distribution.

Typically, newborns are characterized by reduced renal and hepatic clearance at birth (especially with premature birth), which develops rapidly in the first month of life and reaches adult values at 6 months to 1 year of age. Childhood is typically characterized by excellent renal and hepatic clearance, even exceeding that of adults in some cases. Normal clearance values approach that of adults around adolescence. This is an oversimplification, given that different aspects of renal and hepatic clearance develop at different rates. Full reviews of pharmacokinetic differences in children can be found in Kearns et al. [10] and Bartelink et al. [11]. By selecting age-appropriate doses, the pharmacokinetic differences that occur throughout childhood are taken into account. All pharmacists should ensure that medication doses in children are age and/or weight appropriate by consulting neonatal and/or pediatric dosing references with each and every prescription.

Table 28.1 Summary of pharmacokinetic considerations throughout childhood [10, 11]

	Neonates	Infants	Children	Adolescents
Absorption – enteral	Changes in the degree of absorption of some medications due to elevated gastric pH and reduced pool of bile salts Changes in rate of absorption due to prolonged gastric emptying Consider frequent feeds (for medications requiring an empty stomach, this is challenging with q3-4 h feeds) and frequent spit-ups/regurgitation (include counseling on what to do if baby spits up after taking medication)		Biggest factor relates to ability to take medication (related to taste and formulations)	Non-compliance becomes an increasingly important factor
Absorption – other routes	*Rectal* – consider frequent stooling patterns. First-pass metabolism may be bypassed depending on the depth of insertion (lower insertion will bypass first pass metabolism via lower and middle rectal veins, higher insertion still goes through first pass via upper rectal vein) *Percutaneous* – much higher in neonates (especially premature) due to immature keratinization (first 2 weeks of life), high body surface area: volume ratio and high blood flow to skin. Use caution with topical steroids (lowest potency possible)		Similar to adults	Similar to adults
Distribution	Increased volume of distribution for water-soluble medications. Approaches adult values around 6–9 months. Increased CNS permeability in newborn period and early infancy. Reduced protein binding of medications in neonatal period and early infancy (due to altered binding proteins as well as displacing substances such as bilirubin)		Similar to adults	Similar to adults
Metabolism	Reduced (in general) Phase I: CYP3A7 mature at birth, CYP2E1, CYP2D6 mature in around 2 weeks Phase II: sulfation and methylation relatively mature at birth	Variable Phase I: CYP3A4, 2C9, 2C19, 1A2 mature ~ 6 months to 1 year Phase II: glucuronidation mature 2 months to 3 years; acetylation mature in 1–4 years (note other pathways may take over for immature systems, e.g., sulfation of acetaminophen)	Increased (in general); typically exceeding adult values (i.e., frequently require higher mg/kg doses)	Similar to adults
Elimination	Reduced at birth; both GFR and tubular secretion rapidly double in first 1–2 weeks of life	Developing – reaches adult values 6 months to 1 year	Increased (in general) reabsorption matures ~ 2–3 years	Similar to adults

CYP Cytochrome P450

Steps in Assessment

Information Gathering

In pediatric practice, the gathering of patient history is often not done with the patient themselves. Until children are mature enough to provide this information themselves (note that this age varies depending on the child), parents and other caregivers are relied upon to provide an accurate history of the patient's illness(s) and medication(s). This provides an extra challenge to history gathering as the most appropriate person may not be available to provide this history, depending on the circumstances of the child's illness. Changing custody or living arrangements may impact a caregiver's ability to provide a history,

or one parent may be "in charge" of the medical care of the child and another caregiver might happen to be the one present at the time of pharmacists' information gathering. Additionally, information related to symptoms of illness will not be provided first-hand, but rely on observations made by the caregiver. This introduces a source of potential inaccuracy or missing information that is not as commonly encountered when patients provide their own history.

Medical History

While medical histories of children tend to be shorter than that of adults, this is not always the case and many pediatric patients may have long medical histories before they reach school age. Gathering this information is not different than gathering it for adult patients using a combination of patient (caregiver) history corroborated by medical records.

An important difference to note is that in infants (especially those in the first 3 months of life), maternal pregnancy and delivery history is relevant and should be gathered wherever possible as well. Maternal conditions during pregnancy and the circumstances of delivery may be very relevant to an infant's medical care. For instance, a mother using methadone for a substance abuse condition may result in her infant developing signs and symptoms of withdrawal several days after discharge home. Likewise, whether or not a mother received intrapartum prophylactic antibiotics is directly related to the infant's risk of Group B Streptococcus infection in the newborn period. Very few medications are contraindicated in breastfeeding, but knowing if an infant is receiving even small amounts of medications via breastmilk may be relevant if concerns arise regarding a potential drug interactions or adverse effect.

Medication History

As with medical history, medication histories are often shorter in duration and length in children as compared to adults. Again, there are exceptions to this in children with complex medical needs. All relevant details collected for adult medical histories should be collected for pediatric patients, with some additional factors to consider.

Many pediatric medications do not come from the manufacturer in appropriate formulations for administration to children, and thus asking about the formulation is an important step in pediatric medication history. Extemporaneously compounded liquids are especially risky for creating confusion, as often caregivers know the volume they provide to the child but not the concentrations. If there are multiple concentrations available due to variability in the "recipe" followed by the pharmacy during compounding, this can lead to dose errors and subsequent sequelae (see Box 28.1 for an example). If there are any questions regarding the strength of a formulation or volume given, call the pharmacy that provided the previous fill and clarify what was provided. Medications in tablet form (except many sustained or controlled release formulations) may be crushed or dissolved for ease of administration and the appropriateness of this practice should be assessed by the pharmacist depending on the size of the tablet, ease of splitting, and the possibility of alternate dosing intervals (e.g., a daily dose of ASA 20 mg can be delivered as a half tablet [40 mg] every other day instead of a quarter tablet [20 mg] every day). Some medications may be given in a "dissolve-a-dose" manner, whereby a tablet is crushed and suspended in a small amount of liquid, then the dose is measured from the resulting suspension. Certainly, accurate dosing in this situation relies on appropriate suspension of the tablet, and this should be considered when doing an assessment of the patient's dose/response.

Box 28.1 Example of an Error Related to Formulation

There is no commercially available clonidine oral liquid on the market, so it is commonly compounded by pharmacies for use in infants and children who cannot swallow tablets or who require very small doses.

A 10-kg child named Colin is discharged from a hospital with a prescription for clonidine 50 micrograms PO q6h. His parents fill the prescription at the outpatient

pharmacy within the hospital on their way home. The outpatient pharmacy provides them with 500 mL of 10 micrograms/mL compounded clonidine suspension with instructions to take 5 mL four times a day.

Colin's parents go to their neighborhood pharmacy for the next refill. That pharmacy only has a recipe for clonidine 100 micrograms/mL oral liquid and so fills the prescription with that suspension (with instructions to give 0.5 mL four times a day). At home Colin's parents are used to giving 5 mL four times daily and so continue to do so. In a couple of days, Colin is acting lethargic and weak. His parents take him to the nearest emergency department and while they are reviewing the medications with the team, the pharmacist there discovers the error – a 10 times overdose of clonidine.

Even with commercially available appropriate formulations, administration of pediatric medications can be especially challenging. Literature shows that measurement errors are common in caregivers of children and so observing the caregivers measure (and administer if appropriate) the medications may provide insight into dosing appropriateness [12]. Considerations regarding the measurement device should also be made. Household teaspoons are not appropriate for measuring medications, and even some medication syringes do not have appropriate markings for accurate measurement of small doses. Ensuring an appropriate measuring device is an important part of a pharmacist's assessment of dosing accuracy (Fig. 28.1).



Fig. 28.1 Examples of inappropriate (three on left) and appropriate measuring devices

Likewise, how a caregiver gives the medication to the child may be relevant. Medications mixed in a small amount of food/milk immediately prior to administration is appropriate, but if it is mixed in a large amount that the child does not consume all of, the dose taken will not be correct. Medications given on an "empty stomach" or to be avoided with dairy products are not likely to be given according to these restrictions in newborn infants who typically feed every 3–4 hours. In these cases, the medication may be given with feeds (formula or breastmilk) for ease of administration, but a slightly higher dose may need to be used empirically, or the dose may be titrated up based on monitoring parameters (e.g., levothyroxine based on TSH). If this occurs, the administration conditions should be kept consistent for the individual patient, even if "manufacturer recommendations" suggest otherwise. Parents and caregivers may ask if it is appropriate to mix all of a child's medications together in one syringe/cup prior to administration. This practice should ideally be discouraged as it may contribute to inaccurate measurement, potential incompatibilities, and will present challenges with re-dosing or estimating the portion of dosages consumed if only part of the "mixture" is taken/spit-up.

Other things to consider in the medication history of infants and children include medication storage, timing, and palatability. Depending on the frequency of administration of a medication and the child's schedule (school, activities), mediation may not always be stored in an ideal manner. Medications may have to go to the soccer field or to the day home, for instance, and storage conditions may be affected during transitions. The timing of medications may be impacted by adults' schedules or bedtimes. For instance, if a medication is meant to be given every 6 hours around the clock, it may have to be given four

times daily (QID) instead to accommodate bedtimes. Lastly, an assessment of the palatability of the medication formulation and the caregiver's report of how often the child takes/receives their full dose should be completed. These types of issues will be further explored in the section on adherence assessment.

Indication Assessment

Like in the adult setting, "Is this therapy indicated?" is an important question to be assessed by the pharmacist. Due to the relative lack of studies in pediatric patients, often medications that do not have an official indication in pediatrics are used (pediatric use is not included in the product monograph). Because of the lack of appropriate information in the product labeling, alternative data sources need to be accessed to assess the use of the medication in an infant or child. Pediatric medication information sources should be available and reviewed to aid in this part of the assessment, but primary literature may also have to be consulted more often than in adults.

Assessing whether or not an agent is "first-line" or "ideal" for a child includes special considerations that may not be as necessary in adult patients. An agent may be selected not because it has the best data to support it, but because it is the ONLY agent with pediatric dosing information, or because it is the only one with a formulation appropriate for the age group (or it has the best tasting formulation). A medication may be selected because it has a less frequent administration schedule, accommodating a child's school or activity schedule, or to limit the number of dosage times due to unpleasantness of administration (e.g., bad taste or painful injection). In this sense, assessment of whether or not a medication is the most appropriate choice for the patient is increasingly challenging.

Because of differences in pathophysiology or pharmacodynamics in pediatric patients as compared to adults, an "appropriate" or "ideal" medication choice in adults may be quite different in pediatrics. Likely pathogens in bacterial infections differ between age groups, the causes of thrombosis or hypertension are very different in children as compared to adults, and systemic steroids can have very different safety profiles depending on the age of the child. For this reason, complete assessment of whether or not a medication is "indicated" for a child requires much more in depth look into references than for a typical adult patient. Pediatric or neonatal guidelines, reviews, studies, and other literature need to be consulted for this component of the assessment. One cannot rely on what is appropriate in adult patients to be appropriate in newborns, infants, or children.

Dose Assessment

As alluded to above, comprehensive dose assessment in pediatric patients requires several more steps than in adult patients. First, the pharmacist needs to determine how the medication dose is characterized: by gestational age (in newborns), post-natal age, by body weight, by body surface area, or some combination of the above.

Once that is determined, the pharmacist must gather the needed information to categorize the patient into the appropriate dosing range using a pediatric dosing reference. A common error is to use pediatric doses for neonates; therefore, the age of infants needs to be confirmed. In addition to selection of the appropriate dosing category, the pharmacist must also ensure that the appropriate dose for the indication in question is considered. Doses for medications can vary significantly for different indications. For example, the ASA dose for antiplatelet effects is 1–5 mg/kg/day, where anti-inflammatory doses range from 60 to 100 mg/kg/day.

The next step is another common source of error: calculations. Doses should never be estimated and calculations should never be done in the pharmacist's head. A calculator is an essential tool for pediatric pharmacists. Pediatric doses are typically listed in mg/kg/DAY divided qXh, or can be listed as mg/kg/DOSE given qXh. This is a common source of error and must be carefully checked by the pharmacist. While it is common

to see pediatric doses that are higher than adult doses on a mg/kg basis because of the pharmacokinetic differences noted above, it is important to note that adult maximum daily doses (total mg) should typically still be observed in pediatric patients. Box 28.2 provides an example.

Many medications that children use are on a short-term basis only (e.g., antibiotics); however, with medications that are used on an ongoing basis, pharmacists need to ensure that doses are checked with each fill. Children, and especially infants, grow quickly and medications dosed on a mg/kg basis may need adjustment for growth. Each fill is an opportunity for the pharmacist to assess the need to continue a medication, its apparent effectiveness and the presence of any adverse effects as part of the decision as to whether or not to increase the dose (or discontinue it altogether, if appropriate).

Box 28.2 An Example of a Pediatric Dose Approaching an Adult Dose

Rex is a 12-year-old boy being treated for a pneumonia using amoxicillin. He weighs 40 kg.

His prescription states:

$$90\,\text{mg/kg/day} = 1350\,\text{mg PO TID} \times 7\,\text{days}$$

While 90 mg/kg is much higher than most adults would receive, this is an appropriate dose for pneumonia in children. However, the adult maximum daily dose of amoxicillin for pneumonia is 3000 mg, so Rex's dose should be adjusted to 1000 mg PO TID even though this will only be 67 mg/kg/day.

Lastly, the pharmacist needs to identify an appropriate formulation; the one that allows the dose to be measured accurately, is (reasonably) palatable, and has suitable stability. As mentioned above, this may be a significant challenge on its own. As an additional challenge, newborns <44 weeks CGA should ideally not use medications containing preservatives (e.g., benzyl alcohol, propylene glycol) and children should ideally not use medications containing alcohol. This is due to adverse effects reported with these additives (gasping syndrome, metabolic acidosis, hypoglycemia) [13, 14]. However, if an alternative, preservative-free and/or alcohol-free product is not available, the benefit of the medication should outweigh the risks from a small dose of alcohol or preservative.

Monitoring: Efficacy and Safety

Symptom Assessment

In pediatrics, often patients are non-verbal or are not at a developmental stage where they can describe their symptoms and so a caregiver's external assessment of the patients' symptoms must be relied upon. There is a greater focus on *observation* of signs and symptoms when determining a patients need or response to medications. While these observations have some degree of objectivity, many assessments done in this way may include some subjectivity. For this reason, other objective measures may be relied upon more frequently in younger children than in older children or adults. For instance, the objective presence of a fever and results of key lab values (e.g. normalization of white blood cell count) can supplement a parent's subjective report of a child feeling better and acting more "like himself" in an assessment of an infection's response to antibiotics. Pain scoring tools that include a measurement of heart rate, blood pressure, as well as an observation of the infants' behavior can add an objective component to a parent's assessment of their child's pain. There are a variety of pediatric-specific assessment tools for a variety of medical conditions and pharmacists should seek those out when needed. Table 28.2 includes some examples of condition-specific assessment tools for infants and children. It should be noted that dismissing a parent's assessment of their child due to its subjectivity is not advised. Caregivers know typical behavior in their children and slight changes in behavior (e.g., poor feeding, decreased energy, altered sleep) can be important signs of

illness or adverse medication effects in children. Having said that, if subjective observations contradict objective measures, one should proceed with caution. When assessing a child's illness, there are some red flags that should illicit immediate referral to medical care. Table 28.3 depicts a list of the red flag symptoms that prompts referral in pediatric patients.

Table 28.2 Examples of pediatric-specific assessment tools [15–21]

Condition	Assessment tool
Pain	Premature Infant Pain Profile (PIPP) Face, Legs, Activity, Cry and Consolability scale (FLACC) Faces Pain Scale
Sedation	State Behavior Scale (SBS) COMFORT scale
Nausea	Pediatric Nausea Assessment Tool (PeNAT)
Asthma	Childhood Asthma Control Test (C-ACT) (asthma control) Pediatric Respiratory Assessment Measure (PRAM) (asthma exacerbation)

Table 28.3 Red flag symptoms in pediatrics that prompts immediate referral to health care practitioner [22, 23]

System	Symptom
General appearance	Increasing lethargy/confusion
Vital signs	Rash with fever Fever in infant <3 months old Very fast or very slow heart rate (see Table 28.4 for age-based normals) Elevated respiratory rate at rest (see Table 28.4 for age-based normals)
Central nervous system	Change in/loss of consciousness Lack of response to pain Decreased tone/floppiness Seizure-like activity
Cardiovascular	Very fast or very slow heart rate (see Table 28.4 for age-based normal values)
Respiratory	Very fast respiratory rate (see Table 28.4 for age-based normal values) Labored or noisy breathing Irregular or absent respiration
Dermatological	Skin color changes – dusky/blue Very dry lips or mouth
Genitourinary	Severely reduced/lack of urine output

Physical Assessment

Physical assessment in pediatrics can be limited by both the pharmacists' knowledge of the nuances of pediatric physical exam and by the patient's tolerability of the exam itself. It is beyond the scope of this chapter to describe the differences in physical exam between children and adults, but vital sign assessment can be a simple addition to a pharmacists' assessment in many cases, and the major differences between children and adults are summarized in Table 28.4.

Lab Values

As in adults, lab values are an important part of assessing both the efficacy and toxicities of medications in children. Table 28.5 outlines some of the most commonly used laboratory values and how they differ between children and adults.

Monitoring renal function is especially important for pharmacists, both for assessing the need for dose adjustment in renal dysfunction, but also for monitoring for nephrotoxicity of medications. Because normal ranges of serum creatinine in children are relatively wide, serum creatinine values can double, reflecting potential acute kidney injury, but remain in the "normal" range. It is important therefore for pharmacists to follow trends in serum creatinine rather than just absolute values. In cases where the pharmacist needs to estimate renal function, the formula used in children differs from that used in adults. The most accurate and commonly used formula is called the "Bedside Schwartz" formula. Equation 28.1 outlines this important formula. Estimation of GFR in infants and especially in newborns is challenging as renal function continues to develop rapidly after birth, with most infants reaching full renal function around 6 months of age. Again, following trends in serum creatinine (expecting a downward trend in the first 1–2 weeks of life) is the most effective method of assessing renal function. Other factors such as urine output and hydration should also be considered in the overall assessment of renal function. Renal dysfunction in children is fortunately uncommon, and all children with renal dysfunction should be followed by a pediatric nephrology team.

"*Bedside Schwarz*" formula for estimating glomerular filtration rate (GFR) in children >1 year of age [30]:

Table 28.4 Typical normal vital sign ranges, comments on physical exam in children [24–26]

Age group	Normal respiratory rate (breaths per minute)	Definition of tachypnea (breaths per minute)	Comments on pediatric respiratory exam
Newborn	34–50	>60	Respiratory rate is best measured when baby is settled or sleeping, not crying. Increased work of breathing can be indicated by nasal flaring, subcostal and intracostal retraction, head bob, or tracheal tug. Infants and children have narrower airways and a small degree of inflammation can reduce the diameter significantly (e.g., croup). Infants less than a year of age are obligate nasal breathers and nasal congestion can be a significant source of respiratory distress, in addition to being a cause of poor feeding. Noisy breathing including wheeze, stridor, or grunting are signs of respiratory distress and should be referred
Infant	25–40	>50	
Child 1–5 years	20–30	>40	
Child >5 years and adolescents	15–25	>30	
Age group	**Normal heart rate when awake**	**Normal heart rate when sleeping**	**Comments on cardiac exam in pediatrics**
Newborn	100–205	90–160	"Exercise" in infants is best represented by feeding, thus poor feeding/sweating while feeding may be a sign of cardiac compromise. Congenital heart defects are a common cause of cardiac compromise in infants – echocardiography is required to assess heart structure. It is important to assess a child's heart rate at rest and not when they are crying/upset
Infant	100–190	90–160	
Toddler (1–2 y)	100–140	80–120	
Preschooler (3–5 y)	80–120	65–100	
School-age (6–11 y)	75–120	60–90	
Adolescent	60–100	50–90	
Age group	**Normal systolic/ diastolic blood pressure (mmHg)**	**Definition of hypotension – systolic (mmHg)**	**Comments on pediatric blood pressure measurement in pediatrics**
Neonates	70–85/35–55	<60	BP measurement requires pediatric-specific, appropriately sized-cuffs. Definitions of hyper- and hypo-tension require knowledge of the child's age/gender based percentile of height and use of specific blood pressure tables. A quick way to estimate normal systolic blood pressure in a child: median systolic blood pressure = 2(age) + 90 mmHg The most common cause of hypertension in children are renal pathologies, which differs significantly from adults
Infant	70–100/40–55	<70	
Child up to 5 y	90–110/40–70	<70 + (age in years × 2)	
Child >5 y to 11 y	100–120/60–80	<70 + (age in years × 2)	
Adolescent	110–130/65–85	<90	

$$\mathrm{GFR}\left(\mathrm{ml/min/1.73\,m^2}\right) = \frac{36.2 \times \mathrm{Height\,(cm)}}{\mathrm{Serum\ Creatinine}\left(\mu\mathrm{mol/L}\right)} \quad (28.1)$$

Because infectious diseases are commonplace in children, interpretation of bacterial cultures is worth mentioning. Sputum cultures are challenging as contamination with saliva is common. It is therefore necessary to note the presence of endothelial cells and/or nasopharyngeal flora in these cultures as they may indicate a lack of appropriate specimen. Urinary samples, likewise, can be difficult to obtain appropriately without catheterization and thus have a higher likelihood of contamination by skin flora. Lastly, there is a higher rate of false-

Table 28.5 Common lab values used for monitoring medications and how they differ in children [27–29]

Lab value	Normal values	Comments
Hemoglobin	Birth 150–200 g/L Nadir (in term infants) = 90–110 g/L, occurs ~ 6–8 weeks of age Nadir (in preterm infants) = 60–80 g/L, occurs ~ 3–7 weeks of age Normalizes (adult values) ~ 6 months of age	It is normal for infants to have a drop in Hgb following birth, due to a switch from fetal to adult hemoglobin
White blood cells	Neonate 9–30 cells/mm^3 Infant 6–18 cells/mm^3 Child 5–15 cells/mm^3 Adolescence ~ adult values	Newborns may have a decrease in white blood cells in response to infection as cells are used up and replaced at a slower rate
Platelets	Same as adults	Newborns may have slightly lower platelets counts, with a lower limit of 150×10^9/L
Electrolytes	Same as adults	Newborns may have slightly lower sodium (some sodium wasting due to renal immaturity) and higher K (normal state of potassium retention) values than infants and children Serum phosphate also tends to be higher in infants and children due to high needs during bone growth and high energy needs
Creatinine	Newborns 27–88 µmol/L Infants 18–35 µmol/L Children 27–62 µmol/L Adolescents 44–88 µmol/L	Note that creatinine in the first few days of life often reflects maternal renal function, and a downward trend is expected in the first 2 weeks of life

negative blood cultures. Blood cultures in children are typically limited to two bottles (adults typically use four bottles), and use smaller volumes of blood, resulting in a higher risk of false-negative results. The reduced number of bottles also makes distinguishing between pathogenic growth and contamination more difficult. In adults, growth of skin flora in one out of four blood culture bottles is typically associated with contamination; however in children growth of the same pathogen in one out of two bottles is less convincing as contamination. For these reasons, it is not uncommon to empirically treat a child for an infection despite negative cultures, purely based on signs and symptoms of infection. This represents a particular challenge for pharmacists attempting to tailor antibiotic therapy to infectious pathogens. Antibiotic therapy may have to be assessed based on "typical" pathogens rather than actual.

When considering "typical" pathogens, these vary by age and so pharmacists need to consider this when assessing the appropriateness of antibiotic therapy. Another major factor in the "likely" bacteria pathogens is immunization status, and pharmacists should be familiar with vaccination history in patients presenting with infectious diseases. For instance, unimmunized children are at much higher risk of infection with *Hemophilus influenza* type B (HiB), which can be a significant pathogen in both meningitis and pneumonia. Table 28.6 outlines common pathogens in common infections throughout infancy and childhood, assuming vaccination in accordance with local immunization programs.

Adherence Assessment

An assessment of adherence in children should include not only overt nonadherence (e.g., the child dislikes the taste and spits it out, or the parent forgets to give it on the weekends) but also "covert" nonadherence (e.g., parents make measurement errors, or product is used beyond its stability date). Asking to see the caregiver show the dose given as measured, and an examination of the medication bottles can assist with this. Questions regarding the appropriate storage of

Table 28.6 Common pathogens in common childhood infections [31–34]

Infectious disease	Age group	Common pathogens
Meningitis	Newborns	Group B *Streptococcus* *E.coli* Other bacteria, including *Listeria monocytogenes*
	Infants 1–2 months	Group B *Streptococcus* Gram negative bacteria *Streptococcus pneumoniae* *Neisseria meningitides*
	3 months to 9 years	*Streptococcus pneumoniae* *Neisseria meningitides*
	10 years and up	*Neisseria meningitides* *Streptococcus pneumoniae*
Acute otitis media	All ages	Viruses (e.g., respiratory syncytial virus [RSV], parainfluenza, influenza, adenovirus, coronavirus) *Streptococcus pneumoniae* *Non-typeable Hemophilus influenza* *Moraxella catarrhalis* *Streptococcus pyogenes*
Pneumonia	Newborns	Group B Streptococcus Gram-negative enteric bacteria Ureaplasma urealyticum
	Infants <3 months	*Chlamydia trachomatis* RSV Parainfluenza *Streptococcus pneumoniae* *Bordetella pertussis*
	Children ≤5 years	Respiratory viruses (e.g., RSV, parainfluenza, human metapneumovirus) *Streptococcus pneumoniae* *Mycoplasma pneumoniae* (Note that *Staph aureus* can be a common cause of post-influenza pneumonia)
	Children >5 years and up	*Mycoplasma pneumoniae* *Chlamydia pneumoniae* *Streptococcus pneumoniae*
Urinary tract infections	All ages	*Escherichia coli* *Klebsiella* *Proteus* *Enterococcus* *Pseudomonas*

medication are also important (e.g., using coolers for refrigerated medications on long trips).

Measurability

The variability of dosages required for children often make the use of solid dosage forms impractical. If the tablet is appropriate to split, and if a child's dose can be rounded to accommodate a half (or even quarter) tablet, this may be the most practical approach. However, in younger children and for smaller doses, the use of oral liquids may be the only solution. Oral liquids should be measured in appropriately sized devices. Often, especially in infants, doses may be so small that accurate measurement becomes challenging. Doses less than 1 mL are ideally measured in 1 mL (or even 0.5 mL) oral syringes in order to maximize accuracy. Typically, manufacturer guidance dictates that doses <10% of the syringe size cannot be accurately measured (e.g., no less than 0.1 mL in a 1 mL syringe or 0.05 mL in a 0.5 mL syringe).

Occasionally, unique solutions to measurability issues need to be explored. Very small doses of

some injectable products (e.g., enoxaparin doses <10 mg) may be most easily measured using an insulin syringe (e.g., 1 unit = 0.01 mL = 1 mg enoxaparin). Very small doses of oral medications only available in capsules may require (very careful) preparation of powder papers which involves weighing of powders from capsules and packaging in specially folded papers. Whatever the situation, pharmacists must ensure that parents and caregivers using medications in children have an accurate method of measurement available as well as a practical approach to giving the medication.

Palatability

If a medication must be delivered to the child as an unpalatable oral liquid there are some approaches to helping mask the taste of the medication. In infants, most medications can be mixed with a small amount of formula or breastmilk to improve palatability. It is important to instruct parents or caregivers not to mix medications in a full volume of feed (i.e., a full bottle) as the complete dose may not be delivered if the full amount of feed is not taken. Older children may find eating frozen treats prior to taking the medication may numb the tongue enough and reduce the bad taste. Similarly, allowing the child to choose a food or drink to wash the medication taste away may be helpful. Concentrated, sugary beverages or foods (honey, chocolate syrup) or other strongly flavored foods (cheeses) may help mask or remove the taste from the child's mouth.

Medication Administration

Administering oral medications to children can be a significant challenge in itself. After measurement with an appropriate device, oral liquids can be given to infants mixed with a small amount of milk/formula through a bottle nipple, or for older children they can be mixed in a *small amount* of palatable food or liquid before administration. Alternatively, oral liquids can simply be expelled into the cheek (where there are no tastebuds) followed with a drink of palatable liquid. Iron liquid can stain teeth, and so rinsing the mouth is important (can also use a straw if the mediation has been diluted in a liquid). Note that these precautions are unnecessary in infants without teeth, and most important in those with their permanent teeth.

The ability to swallow oral solid dosage forms makes oral medication administration easier, and this can usually occur around age 5 or 6 years. If children struggle with pill swallowing, they can practice with candies with increasing sizes (e.g., start with sprinkles, slowly increasing the size of the candies up to the target tablet size. Usually small jelly beans are sufficiently sized for most medications). Children can place the medication/candy on the back of their tongue, tilt their head back, and have a large drink of liquid to facilitate this. In rare cases, infants and small children can swallow small oral dosage forms with appropriate instruction from qualified professionals. An example is levothyroxine, where crushed tablets and suspensions may not provide the necessary accuracy and part-tablets are the preferred dosage form.

Medications to be administered via feeding tubes (e.g., nasogastric tubes, gastrojejunal tubes) can be administered without palatability concerns; however the intestinal location of the medication administration should be considered in the context of the intestinal administration site (e.g., ensure the medication can be absorbed if administered into the jejunum), and the tubes should be flushed with water afterward to ensure complete delivery of the dose.

Adolescents

As a final comment on adherence assessment, it is important to consider adolescents specifically. Increasing independence with medication use and administration is often given to adolescents as they move toward adulthood, which requires a change in the pharmacist's approach. Where previously assessment was conducted primarily with the caregivers on behalf of the child, the pharmacist should begin to include the adolescents in these conversations in an attempt to build their health literacy and knowledge of their conditions/medications. Also of note, adolescents often become more self-conscious of their medical conditions and associated medication use, and strategies to increase the discreteness of

Table 28.7 Pediatric assessment steps, common errors, and tips to avoid errors

Step in assessment	Common errors	Pediatric considerations
1. Information gathering	Caregivers confusing mg with mL when stating dose Unknown or incorrect concentration dispensed	Try to take history from most appropriate caregiver. Include maternal history if <3 months of age Include formulation, strength, and administration details in medication history
2. Indication assessment	Unfamiliarity with pediatric indications	Be sure to use pediatric references Consider "other" reasons for selection of agent-administration schedules, palatability, and availability of pediatric data
3. Dosage assessment	Mathematical errors Using dose for wrong age group mg/kg/day vs mg/kg/dose Exceeding adult daily maximum dosage Patients outgrowing doses of chronic medications	Use neonatal doses for neonates, age appropriate pediatric doses for infants and children Check dose for specific indications Double check math Consider growth with medications used chronically Keep adult maximum daily doses in mind
4. Efficacy and safety assessment	Unfamiliarity with pediatric "normal" values for physical exam or laboratory parameters	Try to include objective and subjective measures Physical exam, laboratory values, assessment of renal function, and typical pathogens may differ from adults
5. Adherence assessment	"Covert" non-adherence (parents inappropriately measuring medications or using compounded medications beyond expiry date)	Ensure caregivers have a practical approach to measurement and administration of the required doses Assess for palatability issues Observe measurement and/or administration of medications by caregivers Help transition adolescents to adulthood and independent medication use

their medication use may be appreciated and improve adherence. For example, selection of a dry powder inhaler instead of a metered-dose inhaler with spacer device, or choosing a once or twice-a-day administered agent instead of one that has to be used at school. Considerations such as these should come into a pharmacist's assessment as their pediatric patients move toward adulthood.

Assessing medication use in children has many similarities to that in adults, and should be approached in a similarly systematic way, bearing slight nuances in mind. Table 28.7 summarizes the approach to pediatric assessment, highlights common sources of errors, and provides some tips for minimizing these errors.

Clinical Pearls

- Assessment of dose requires additional steps in children as compared to adults – categorization by age/weight, calculation of appropriate dose, and determination of accurate measurement processes are a few major steps that need to be included.
- Infants and children have variable pharmacokinetic and pharmacodynamic parameters, and thus dosages vary widely. The use of pediatric/neonatal references is essential for appropriate dosing and indication assessment by pharmacists.
- Finding appropriate formulations for children is a challenge for pharmacists. Careful assessment

of doses/concentrations, measurability, and method of administration need to be included in the overall medication assessment for infants and children.

- Interpretation of diagnostic tests and vital signs varies in children and a basic understanding of these differences is important for pharmacists assessing children medication therapy.

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Women's Health

29

Nese Yuksel

Chapter Objectives

1. Describe the goals of therapy and management strategy for menopause.
2. Assess women for menopausal symptoms and who may be considering hormone therapy.
3. Describe the goals of therapy and therapeutic options for women seeking hormonal contraceptives.
4. Assess women who are seeking combined hormonal contraception.

Assessment of the Menopausal Woman

Background

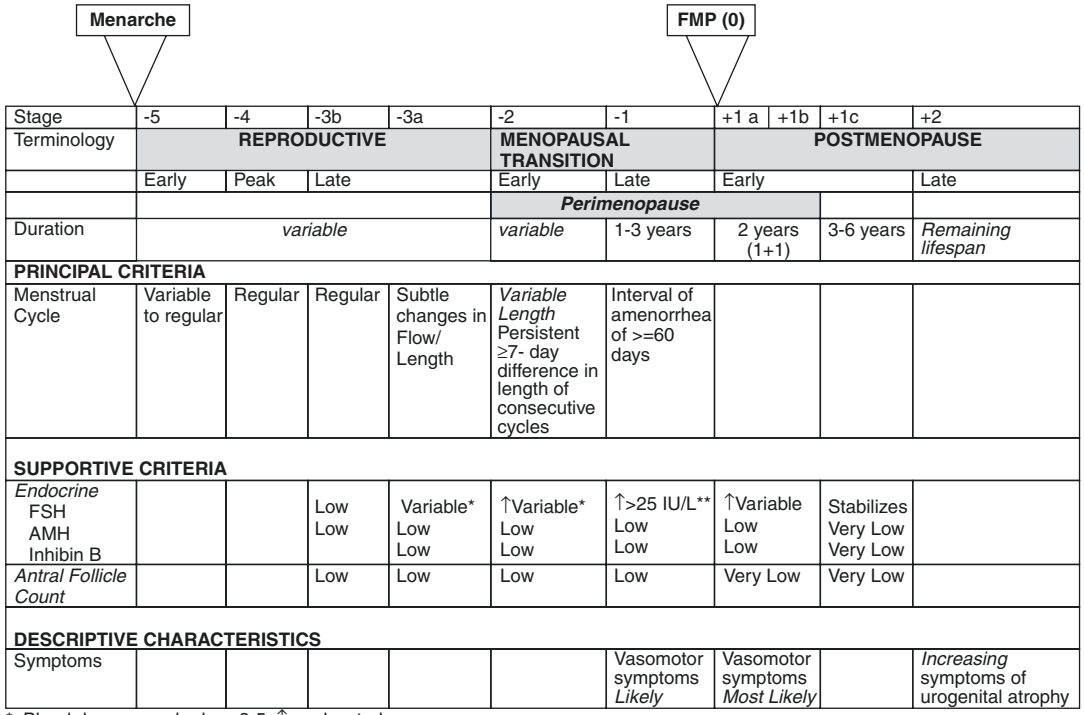
Menopause is part of the normal aging process and is defined as the cessation of menstruation due to the loss of ovarian function. The average age of menopause in North America is 51 years (45–55 years) [1]. The menopause transition or perimenopause is the time leading up to the menopause. The Stages of Reproductive Aging Workshop (STRAW+10) classification depicts the stages of menopause, which are classified according to changes in a woman's menstrual patterns and follicle stimulating hormone (FSH) (Fig. 29.1) [2]. Many women start having symptoms, with or without menstrual cycle changes, during the menopause transition. Hormone levels fluctuate and decline during the menopause transition, with symptoms starting up to 8 years before the last menses.

Menopause can be a natural process or induced through surgery (bilateral oophorectomy), chemotherapy, or radiation. Menopause before the age of 45 years is considered early, while premature menopause occurs before the age of 40. The early loss of estrogen before the natural age of menopause increases the risk of long-term health consequences such as cardiovascular disease (CVD), osteoporosis, cognition and dementia, and early mortality.

The most common menopausal symptoms are vasomotor (hot flashes, night sweats), genitourinary, sleep disturbances, and muscle and joint pain (Table 29.1). Approximately 80% of women will have vasomotor symptoms (VMS), while 25% will be severe enough to affect quality of life [1]. Genitourinary syndrome of menopause (GSM) captures the range of urogenital symptoms associated with estrogen deficiency, including vaginal dryness, urinary incontinence, recurrent urinary tract infection, and dyspareunia. GSM affects more than 50% of postmenopausal women [3].

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* Blood draw on cycle days 2-5 ↑ = elevated

** Approximate expected level based on assays using current international pituitary standard[67-69]

Fig. 29.1 Stages of Reproductive Aging Workshop (STRAW+10). (Reprinted with permission from Wolters Kluwer Health, Inc. Harlow et al. [2])

Table 29.1 Menopause symptoms

Classification	Types of Symptoms
Vasomotor	Hot flashes Night sweats
Genitourinary	Vaginal dryness Urge/stress incontinence Dyspareunia Frequent urinary tract infections
Sleep	Fragmented sleep Insomnia
Mood Symptoms	Anxiety, irritability, depressive symptoms, mood swings
Musculoskeletal	Stiffness/soreness Muscle/joint pains
Memory/ concentration	Memory changes Difficulty concentrating/focus
Sexual	Low libido
Others	Fatigue Headaches/migraines Dry skin/eyes Heart palpitation

This chapter focuses on the assessment required for the management of menopausal symptoms. The period of midlife is also an opportune time to review long-term health risks such as CVD, osteoporosis, and breast cancer.

Diagnosis

Natural menopause is diagnosed when a woman has not had a menstrual period for 12 months. With the loss of ovarian function, the levels of estrogen and progesterone fall, resulting in a subsequent increase in FSH levels. There are no specific diagnostic tests for menopause, but an elevated FSH level will help confirm the diagnosis when a woman has not had a menstrual period for 12 months or longer. In women who have had a hysterectomy before the cessation of ovarian function, hormone levels (estrogen, progesterone) and FSH are helpful in determining menopause status. Perimenopause is associated with fluctuating hormone levels, and FSH levels can be variable and erratic; these measurements should not be used for diagnosis.

Treatment Approaches

Menopausal hormone therapy (HT) is the treatment of choice for moderate to severe menopausal symptoms. HT should be individualized to the woman after consideration of the woman's benefits and risks (Table 29.2). Many women worldwide discontinued HT after the initial publication of the Women's Health Initiative (WHI) in 2002 showed an increased risk of coronary heart disease (CHD), stroke, and breast cancer with estrogen and progestogen [4]. However, these results have been recently questioned, as many outcomes in the study (such as CHD, breast cancer) were not statistically significant [5]. The estrogen-alone arm of the WHI study did not show the same risks of CHD or breast cancer [6]. Current professional guidelines agree that systemic HT is safe and effective for initiating in women less than 60 years of age or less than 10 years postmenopause [1, 7, 8]. Hormone therapy also reduces osteoporotic fractures and is an option for the treatment of osteoporosis in women who have concurrent menopausal symptoms [9].

The current recommendations for symptom relief are to continue systemic HT for as long as the women needs it for symptoms [8]. For early or premature menopause, HT is recommended until the average age of menopause, not only for symptom relief but also for prevention of osteoporosis, CVD, and cognitive changes [7, 8]. In women with an intact uterus, estrogen is provided along with a progestogen to reduce the risk of endometrial cancer. Progestogen refers to both synthetic progestins and natural progesterone. Another option is the use of a tissue-selective estrogen complex (TSEC), which uses a selective estrogen receptor modulator (bazedoxifene) for endometrial protection in combination with an estrogen. Women who have had a hysterectomy can use estrogen alone.

The management of perimenopause may differ slightly. Options include combined hormonal contraception (if irregular or heavy bleeding or if contraception is required), hormone therapy, or estrogen in combination with a levonorgestrel-intrauterine system (LNG-IUS). The need for contraception during the perimenopause should also be considered.

Non-hormonal prescription medications for vasomotor symptoms include antidepressants (selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, citalopram, and escitalopram, serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and desvenlafaxine), gabapentinoids (i.e., gabapentin, pregabalin), and clonidine. These medications are not as effective

Table 29.2 Benefits and risks of hormone therapy

Type of HT regimen	Benefits	Risks	Considerations
Systemic estrogen alone	Relief of menopausal symptoms Prevention of bone loss and reduce osteoporotic fractures Improve quality of life	Venous thromboembolism (VTE) Cardiovascular disease (CVD) Stroke Gallstones Note: increase in breast cancer was not seen in large randomized trials such as WHI estrogen therapy-alone arm	Age (≥60 years) and time since menopause (≥10 years postmenopause are risk factors for VTE, stroke, and CVD when *initiating* HT) Greatest risk of VTE is in the first 1–2 years Transdermal estrogens at standard doses may have less risk of VTE
Systemic estrogen and progestogen	Same as estrogen alone	Venous thromboembolism (VTE) Cardiovascular disease (CVD) Stroke Breast cancer Gallstones	Same as estrogen alone Progesterone may have less risk of breast cancer compared to synthetic progestins; however this data is primarily from observational data
Local vaginal estrogen therapy	Relief of GSM symptoms	Not the same risks as systemic estrogen	Low systemic estrogen levels as long as standard doses are used

CVD cardiovascular disease, *GSM* genitourinary syndrome of menopause, *HT* hormone therapy, *VTE* venous thromboembolism; *WHI* Women's Health Initiative

as HT for vasomotor symptoms; however, they may be an option in women who have contraindications to or choose not to take HT [10].

For mild vasomotor symptoms, alternate approaches include phytoestrogens (e.g., soy-based products), natural health products (e.g., black cohosh), or non-pharmacologic approaches including lifestyle measures (e.g., weight loss, avoiding triggers), acupuncture, mindfulness, and cognitive behavioral therapy (CBT). Though studies have shown mixed results, there is some compelling evidence for weight loss, mindfulness, and CBT.

Local vaginal estrogen therapy is preferred for GSM. Vaginal estrogens have very little systemic absorption and can be used in women with contraindications to systemic estrogen. In women with estrogen receptor positive breast cancer, vaginal estrogen should only be considered if other non-hormonal therapies have failed and only after careful consideration of risks and benefits in consultation with an oncologist [11]. Non-pharmacologic options for GSM include lubricants, moisturizers, vaginal dilators, and pelvic floor physiotherapy [11].

Patient Assessment

Pharmacists play an important role in assessing women for menopausal symptoms, discussing options, reviewing the risks and benefits for each of the options, including HT and managing the care of these patients. As with any patient care process, the initial assessment begins with a complete relevant history including demographics, medical history, social history (smoking, alcohol use), family history (e.g., family history of breast cancer, cardiovascular disease), medications (prescription and non-prescription), laboratory and physical exam findings. The following information should be collected specifically for the care of women suffering from menopausal symptoms.

Gynecologic History

The purpose of the gynecologic history is to capture the menopausal status of the woman (peri- or postmenopausal), to determine if the woman has had a hysterectomy or bilateral oophorectomy, and to identify if she is experiencing any issues with her menstrual periods or vaginal bleeding if the uterus is still intact. In a perimenopausal woman, it is important to capture menstrual regularity, cycle length, flow, or any other issues with her periods. Questions to ask include:

Are you still having menstrual periods?
If no:
Did you have a hysterectomy? When did you have your hysterectomy?
Have you had your ovaries removed (one or both)? When did you have the surgery?
When was your last menstrual period?
Are you having any vaginal spotting or bleeding (if uterus still intact)?

If yes, still having periods:
Are you having any changes in your menstrual patterns?
Are your periods regular or irregular?
How often do you get your periods?
Are your periods heavy or light? How long do the periods last?
Are your periods painful?
Do you get spotting or bleeding in between periods?

Consider the need for contraception if the last menstrual period was <2 years for woman less than 50 years or <1 year if older than 50 [12].

Are you sexually active? Do you need contraception?
What contraception do you currently use?

Menopause Symptom History

A good symptom history is important in capturing the type of symptoms experienced, the severity, how bothersome the symptoms are to the woman and the impact on the woman's quality of life.

For each symptom, it is important to ask:

What symptoms are you having? (see Table 29.1 for symptoms).
How often are you having the symptoms?
How would you describe the severity of these symptoms (for example on a scale of "mild to severe" or "not at all to extremely")?

When did the symptoms start? Are they worse at certain times of the day or in certain parts of your cycle?
How long do the symptoms last? A hot flash can last from 1–5 minutes. If longer than this, consider other possible causes of hot flashes.
Is there anything that makes the symptoms worse?
How are the symptoms affecting your quality of life?
For genitourinary symptoms, are you having pain with intercourse?

Medical History

A comprehensive personal medical history is important when assessing menopausal women for several reasons: (1) to identify diseases or drugs that may lead to symptoms overlapping with menopausal symptoms; (2) to identify long-term health consequences which may need preventative measures or treatment such as osteoporosis, hypertension, hyperlipidemia, or other cardiovascular diseases; and (3) to capture contraindications to HT and other medications. Conditions or medications that may contribute to VMS should be identified initially and dealt with if appropriate prior to treatment (Table 29.3). Contraindications to HT include:

- Unexplained vaginal bleeding
- Known or suspected breast cancer
- Active liver disease
- Active venous thromboembolism
- Acute cardiovascular disease
- Cerebrovascular accident
- Pregnancy

Capturing other comorbidities is important to identify if women have further risks for venous thromboembolism (VTE), CVD, and stroke, as well choosing among the different hormone therapy options. Comorbidities that are important to consider include [13]:

- Obesity
- Smoking
- Hypertension
- High lipids
- Diabetes

Table 29.3 Medical conditions and medications that can cause vasomotor symptoms

Medical Conditions	Hyperthyroid Hyperparathyroid Carcinoid tumor Pheochromocytoma Lymphoma
Medications	Raloxifene GnRH agonists Aromatase inhibitors Nicotinic acid (niacin) Opiates Calcium channel blockers Chemotherapy Antipsychotics Some antidepressants (e.g., SSRI)

GnRH gonadotropin-releasing hormone, *SSRI* selective serotonin reuptake inhibitor

- Other CVD risk
- Gallstones

Symptom Management

Many women will try a number of measures such as lifestyle changes, non-pharmacologic options, or natural health products before seeking help from a health-care provider. Identifying if the woman has tried HT or non-hormonal medications is also helpful. The following are questions to ask:

What have you tried to help your symptoms (including lifestyle factors, herbals, vitamins, other medications)?
Are you currently taking hormone therapy or have you tried in the past?
What has helped with your symptoms?
What was the name of the product? What dose did you use?
How long did you try it? Was it effective for you?
Why did you stop?
Did you experience any side effects?

Additional Assessment Considerations

- An elevated FSH can help confirm menopause in the postmenopausal women. In the perimenopause, FSH and estrogen levels fluctuate and are not diagnostic.

- Other laboratory testing includes a TSH level as symptoms from low thyroid levels can overlap with menopause symptoms.
- Women who have undiagnosed abnormal uterine bleeding should be referred. Check to see if they have had a pelvic ultrasound and/or endometrial biopsy completed.
- Assessment of CVD risk includes checking blood pressure, lipids, and glucose.
- Establish when and the results of the last pap smear and mammogram, as these should be completed according to local guidelines.
- BMD measurement can be considered if the criteria for BMD testing are met (see Chap. 18 "Osteoporosis").

Decision-Making with Hormone Therapy

Menopause can be a confusing time for women, and decision-making regarding HT may feel complex. Communicating in a balanced way about the benefits and risks of HT is important for informed decision-making (see Table 29.2) [1, 8]. Systemic HT has a number of benefits including relieving vasomotor symptoms, helping with sleep, and improving quality of life. For GSM alone, vaginal estrogen therapy can be considered. Approximately 40% of women on systemic HT continue to have GSM symptoms; therefore vaginal estrogen therapy can be considered in combination with systemic HT. Choosing among the systemic HT products will be dependent on patient preference, as well as patient-specific factors. Estrogen is given continuously every day, and the progestogen is given continuously every day or cyclically (12–14 days every month). See Table 29.4 for HT products in Canada and common doses. Transdermal estrogen does not have a high first-pass effect through the liver, and at standard doses, may have less risk of VTE compared to oral at standard doses. Transdermal estrogen may be preferred over oral estrogen in women who are smokers, with

Table 29.4 Hormone therapy products in Canada

Formulation	Type of estrogen	Starting doses
Estrogen		
Oral	Conjugated estrogen (CE) 17ß-Estradiol	0.3–0.625 mg tablet daily 0.5–1 mg tablet daily
Transdermal patch	17ß-Estradiol	25–50 µg patches once or twice weekly (depending on product)
Transdermal gel	17ß-Estradiol (gel)	1–2 metered doses/actuation daily 0.5–1 mg packets daily
Progestogen		
Oral	Progesterone micronized	100 mg daily for continuous regimen 200 mg daily for 12–14 days every month for cyclic regimen
Oral	Medroxyprogesterone acetate	2.5 mg daily continuous regimen 5 mg daily for 12–14 days every month for cyclic regimen
Oral	Norethindrone acetate	5 mg daily
Combination of estrogen and progestogen products		
Oral	17ß- Estradiol/norethindrone acetate	1 mg estradiol/0.5 mg norethindrone tablet daily 0.5 mg estradiol/0.1 mg norethindrone tablet daily
Oral	17ß-Estradiol/drospirenone	1 mg estradiol/1 mg drospirenone tablet daily
Transdermal patch	17ß-Estradiol/norethindrone acetate	140/50 (50 µg estradiol/140 µg norethindrone) twice weekly 250/50 (50 µg estradiol/250 µg norethindrone) twice weekly
Tissue-selective estrogen complex (TSEC)		
Oral	Conjugated estrogen (CE)/ bazedoxifene	0.45 mg CE/20 mg bazedoxifene tablet daily

high triglyceride levels, low libido, and gall bladder disease.

Monitoring Hormone Therapy

Women should be asked about improvements in symptoms, as well as breakthrough bleeding and adverse effects on follow-up. Common adverse effects with estrogen include breakthrough bleeding, breast tenderness, water retention, and headache. Progestogen adverse effects include mood changes such as depression and anxiety, irritability, headache, breast tenderness, and water retention. Natural progesterone may cause drowsiness. Breakthrough bleeding, one of the most common reasons for early HT discontinuation, can occur up to 6 months after starting HT. Other common adverse effects will improve with time. Breakthrough bleeding in a postmenopausal woman that occurs after 1 year on HT will require further investigation and should be referred. Adverse effects of estrogen that continue to be bothersome can be managed by changing to a lower dose or switching product formulations. Progestogen side effects can be handled by changing to a different progestogen, switching to cyclic if on continuous, or using LNG-IUS instead. There is no time frame for HT discontinuation in the post-menopausal woman, current guidelines recommend to continue HT for the time that the woman needs it for symptom relief [8].

Assessment of Women for Hormonal Contraception

Background

It is estimated that 40% of all pregnancies in Canada are unintended, and nearly a half are from women on some form of contraception [14, 15]. Unintended pregnancy results in adverse maternal and child health outcomes, as well as significant costs to the health-care system [15]. When helping women select among the contraceptive options, considerations include effectiveness of the contraceptive method (typical failure rates), ease of use, access, cost, and patient-specific factors. Tailoring the contraceptive method to the individual needs is important for the woman's commitment to the chosen method and continued adherence. Adherence to contraceptives is poor, with 60% of women using incorrectly or inconsistently [16]. Long-acting reversible contraceptives (LARC) such as the intrauterine devices including levonorgestrel intrauterine system (LNG-IUS) have the highest effectiveness and continuation rates as their use does not require regular action by the user [17]. Contraceptive options include both non-hormonal methods (barrier contraceptives) and hormonal contraception. Efficacy rates for the various contraceptive methods can be found in Fig. 29.2.

Hormonal Contraceptive Options

Hormonal contraceptives refer to both combined hormonal contraceptives and progestin-only contraceptives. Combined hormonal contraceptives (CHC) contain an estrogen (ethinyl estradiol) and a progestin and are available as combined oral contraceptives (COC), transdermal patch, and vaginal ring. CHCs can be safely used in healthy women after careful consideration of contraindications. In addition to preventing pregnancy, CHCs have many non-contraceptive benefits and are used for a number of other conditions (Table 29.5).

The LNG-IUS is an intrauterine device that slowly releases a progestin (levonorgestrel) directly into the uterus. LNG-IUS is especially favorable as a LARC as it is as effective as permanent contraception. Current guidelines recommend LARCs such as LNG-IUS as a first-line contraceptive option for women [14]. LNG-IUS also have other non-contraceptive uses including abnormal uterine bleeding, dysmenorrhea, endometriosis, and providing endometrial protection for women on estrogen alone.

Progestin-only contraceptives include the progestin-only pill and depot injection (depot medroxyprogesterone acetate). Progestin-only contraceptives are options in women where estrogens may not be appropriate such as smokers over age 35, postpartum (≤6 months) or breastfeeding.

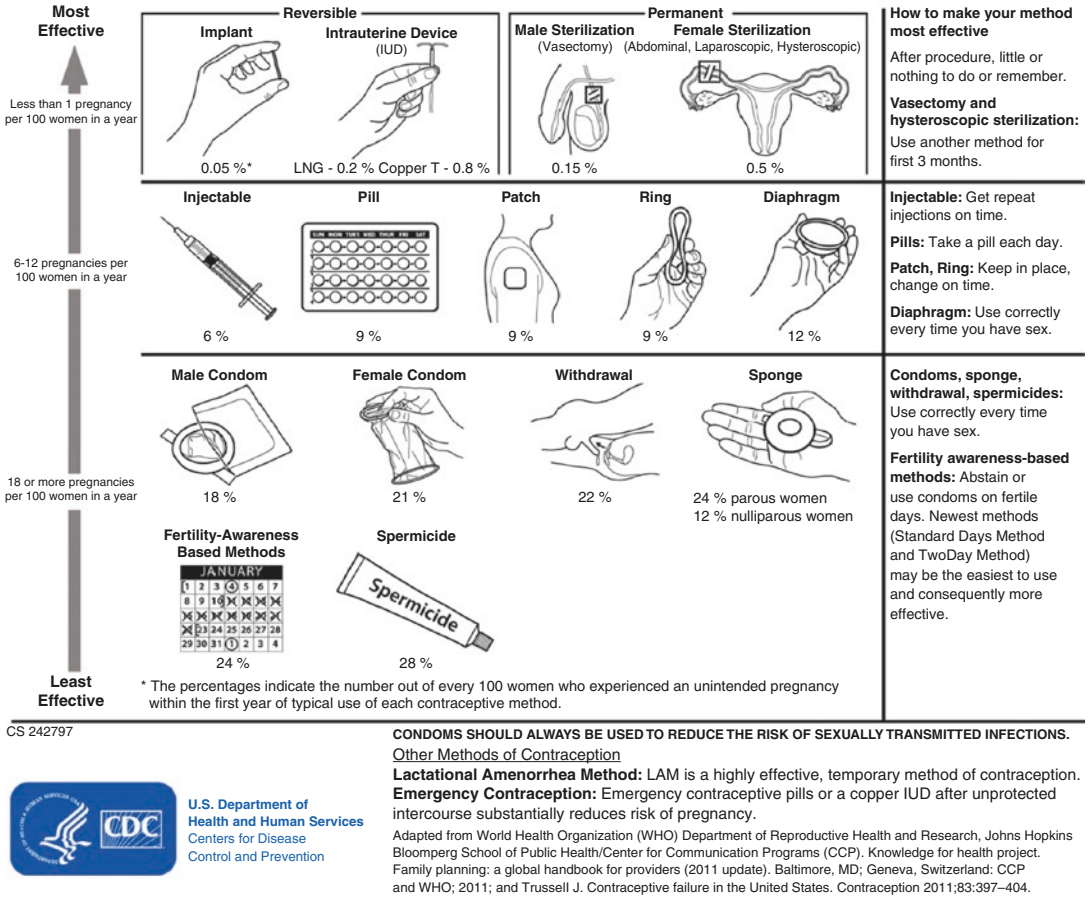


Fig. 29.2 Effectiveness of Family Planning Methods. Available at https://www.cdc.gov/reproductivehealth/contraception/unintendedpregnancy/pdf/Contraceptive_methods_508.pdf (Accessed July 27, 2018). The use of the material does not imply an endorsement by the Centers for Disease Control and Prevention (CDC) or Health and Human Services (HHS) of any particular organization, service, or product and that any views expressed in the book do not necessarily represent the views of CDC or HHS

Table 29.5 Non-contraceptive benefits of CHC

Menstrual-related benefits
Decreased menstrual blood loss and anemia
Decreased dysmenorrhea
Reduced PMS symptoms
Others
Decreased acne
Improved hirsutism
Improved bone health
Perimenopausal symptoms
Prevention of ovarian and endometrial cancer

CHC combined hormonal contraceptives, *PMS* premenstrual syndrome

This chapter focuses on the assessment of CHC as these agents are one of the most commonly used methods of contraception by women. In Canada, the use of COC is second only to the use of condoms [18].

Patient Assessment of CHC

Pharmacists play an important role in assessing women for CHC, discussing options and reviewing the risks and benefits for each option. As with any patient care process, the initial assessment begins with a complete relevant history including demographics, medical history, social history (smoking, alcohol use), family history, medications (prescription and non-prescription), laboratory and physical exam findings. The following

information should be collected specifically for women seeking CHC.

Reasons for CHC

A woman may be interested in CHC for other reasons than contraception. Inquiring about other reasons that the woman may be considering CHC is important (see Table 29.5). Additionally, she may also not be aware of non-contraceptive benefits, which would be important to discuss when counseling.

If the woman is primarily interested in contraception, it may be an opportune time to discuss the benefits of long-acting reversible contraceptives such as LNG-IUS prior to the CHC assessment. LNG-IUS may be a good option to consider, if the woman is not planning on getting pregnant in the next year and has no other contraindications. If the woman is interested in an LNG-IUS, then refer her to her physician.

Menstrual History

A good history captures baseline information on a woman's menstrual cycle. The possibility of pregnancy should be ruled out before considering CHC. Any undiagnosed abnormal uterine bleeding should be identified and the woman referred to her physician.

When was your last menstrual period?
How often do you get your periods? Are they regular or irregular?
Are your periods heavy? How long do they last?
Do you get spotting or bleeding in between periods? Has this been assessed?
Have you had unprotected intercourse since your last menstrual period? If there is a possibility that the woman is pregnant, recommend a pregnancy test and refer to physician.

Medical History

A comprehensive medical history is important to identify CHC contraindications and to help choose among the different contraceptive options.

Table 29.6 Absolute contraindications to CHC (WHO Medical Eligibility Criteria Category 4) [19]

Smokes >15 cigs/day and over 35 years of age
Cardiovascular disease
History of hypertension (not controlled)
History of stroke
History of migraines with aura
Diabetes with microvascular complications
Venous thromboembolism – current or past
Thrombophilia
Breast cancer history – current or past
Active or past liver disease
Given birth in the last 3 weeks
Breastfeeding <6 weeks postpartum
Rheumatic diseases such as lupus
Other active cancers/chemotherapy

CHC combined hormonal contraceptives, *WHO* World Health Organization

See Table 29.6 for the World Health Organization contraindications to CHC [19]. Special attention is needed for capturing cardiovascular risk factors (smoker, obesity, high lipids, hypertension, diabetes, and history of CVD), breast cancer risk, and liver disease. Questions to ask during the history include:

Do you smoke? CHC are contraindicated in women over the age of 35 years who smoke.
What is your weight? Measure the woman's weight to get a baseline. Determining weight/BMI is helpful in choosing among the hormonal contraceptives (see Decision Making). The risk of VTE is also increased in obese women.
Do you suffer from migraines? Are they associated with an aura? Migraines with aura are associated with a higher risk of stroke compared to women without migraines. CHC should not be used in women with migraines with aura.
Have you had a blood clot in the past? CHC is associated with an increased risk of VTE. A history of VTE is a contraindication to the use of CHC.
What medications are you currently taking? Current medication list will be important to screen for possible drug interactions with CHC. Medications of most concern are inducers of cytochrome P450 CYP3A4 including anticonvulsants, rifampin, some antiretrovirals and the natural health product, St John's wort.

It will also be important to identify if the woman is recently postpartum, if she is less than 6 weeks postpartum and breastfeeding she is not a candidate for CHC, while less than 6 months is a

relative contraindication [19]. Progestin-only contraceptives should be considered in both of these scenarios.

Past Contraceptive Use

It is important to capture the types of contraceptives (both non-hormonal and hormonal methods) that have been used in the past. Time frame, duration of use and experience with the contraceptive method, as well as any side effects experienced will help in CHC decision-making.

What type of contraception are you currently using?
Have you been on hormonal contraception in the past? Which ones and for how long?
How satisfied were you with this method?
Did you have any side effects?

Physical Assessment

A blood pressure measurement should be performed at baseline prior to initiating CHC. If the blood pressure is ≥140/90, the woman should be referred to their physician. A Pap smear, pelvic examination, or STI testing are not needed prior to starting CHC. These can be completed as part of routine healthy women's care but are not necessary before starting CHC.

Decision-Making with CHC

In the absence of contraindications, deciding among the CHC options is dependent on the woman's preference, as well as previous CHC experience. The CHCs vary with the doses of ethinyl estradiol (10–35 μg ethinyl estradiol), the types of progestins, dose regimens (monophasic, biphasic, triphasic), and the formulation (oral, transdermal patch, vaginal ring). Phasic formulations (e.g., triphasic) were formulated to decrease the exposure to progestins; however, it is unclear if they provide any advantage over monophasic products. The progestins have different progestogenic, androgenic, and estrogenic properties. First-generation (e.g., norethindrone) and second-generation progestins (e.g., levonorgestrel) may have lower VTE risk compared to other progestins; however, this is controversial. Current Canadian guidelines do not recommend preferential prescribing of the type of progestin in CHCs [20]. The classic CHC regimen is 21 days of the CHC, followed by 7 days of hormone-free intervals (21/7). Several products are now available with shortened hormone-free intervals (HFI) of 4 days (24/4) or with estrogen only during the HFI. Continuous (i.e., daily dosing with no HFI) or extended dosing of CHC (i.e., 7-day HFI every 3 months, 84/7) may be considered in women who have symptoms during the HFI (e.g., headaches, pelvic pain, endometriosis, PCOS) or do not want to have withdrawal bleed. If considering continuous or extended CHC regimens, use monophasic products or extended dosing-specific formulations.

The CHC patch or ring may be preferred in women who want the convenience of weekly application (patch is applied once a week for 3 weeks followed by 7-day HFI) or monthly administration (ring is inserted for 3 weeks followed by 7-day HFI). The CHC patch should be avoided in women over 90 kg. Most studies with oral contraceptives do not indicate a decrease in contraceptive efficacy with obesity, but this is not clear in all studies. As a decrease in effectiveness cannot be ruled out in women with BMI ≥30 and as obesity is associated with increased VTE risk, the LNG-IUS may be a consideration in obese women [20].

This is a good time to ask about the woman's familiarity with non-hormonal contraceptives (i.e., barrier methods) as well to prepare for counseling of prevention of sexually transmitted infections and recommendations for back up contraception for missed CHC.

Monitoring Hormonal Contraceptives

Ideally it is best to have follow-up 1–3 months after the woman has started the CHC. On follow-up, the woman should be asked about her satisfaction with the method, as well as breakthrough bleeding and adverse effects (Table 29.7). If

Table 29.7 Adverse effects of CHC

Estrogen-related	Estrogen deficiency	Progestin-related	Progestin deficiency
Nausea Headaches Breast tenderness Fluid retention Poor contact lens fit Chloasma	Early/midcycle BTB Hypomenorrhea Menopausal symptoms (vasomotor, insomnia) Mood (irritability, depression)	Breast tenderness Fluid retention Bloating Mood (anxiety, depression) Headache Appetite changes	Late BTB/spotting Heavy menstrual flows Delayed menses

CHC combined hormonal contraceptives, *BTB* breakthrough bleeding

using for other non-contraceptive benefits as well, inquire about symptom improvement. Inquire about her adherence and if she is having any issues with adherence. Blood pressure should be repeated. It is also a good time to assess if the woman has any changes in health status (i.e., new medications, new medical conditions).

Clinical Pearls

Menopause

- Pharmacists play an important role in assessing women for menopausal concerns.
- Assessment of women for menopausal concerns includes gynecologic history to capture menopause status, experience of menopausal symptoms, impact on quality of life, and detailed medical history to capture contraindications or risks to medication options.
- Hormone therapy is a safe and effective option when initiating in women younger than 60 years of age or within the first 10 years of their last menstrual period and after careful consideration of benefits and risks.

Contraception

- Pharmacists play an important role in assessing women for contraceptive care.
- Assessment of women for combined hormonal contraceptives (CHC) includes history of menstrual cycles, previous use and experience of contraceptives, and detailed medical history to determine if there are any contraindications or risks to using CHC.
- CHC are safe to use in healthy women of reproductive age who do not have contraindications.

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Anemia Assessment

30

Christine A. Hughes

Chapter Objectives

1. Describe the classification of anemia.
2. Complete a patient assessment and interpret laboratory findings to determine the most likely cause of anemia.
3. Apply a monitoring and follow-up plan for patients initiated on treatment for anemia.

Background

Anemia is commonly encountered in clinical practice and is characterized by a decrease in hemoglobin (Hgb) or red blood cells (RBCs) resulting in reduced oxygen carrying capacity of the body [1] . Anemia is defined by the World Health Organization as a Hgb < 130 g/L in adult men, <120 g/L in non-pregnant adult women, and <110 g/L in pregnant women [2]. Severe anemia is a Hgb < 80 g/L in adult men and non-pregnant women [2]. It is important to note that Hgb values vary based on gender as well as ethnicity. As examples, women typically have lower Hgb concentrations than men, and African-Americans have lower values as compared to Caucasians [1].

Anemia can cause significant morbidity and mortality. Older adults with anemia have higher hospitalization and mortality rates, while anemia in children can impair cognitive and psychomotor development. Globally, anemia impacts approximately 25% of the world population [1]. In the United States, estimates suggest almost 6% of the population has anemia, with certain groups such as the elderly or pregnant women at higher risk [3].

Given the prevalence of anemia, pharmacists play an important role in assessing patients with anemia, determining potential cause(s), and identifying the need for additional laboratory testing or referrals where appropriate. Pharmacists can also assist patients with treatment options, dietary recommendations, and managing drug-drug interactions with oral iron supplements.

Clinical Presentation

Sign and symptoms of anemia can vary considerably depending on factors such as the rate of development and overall health status of the patient [4]. In many cases, mild anemia is asymptomatic and may be found when ordering a complete blood count (CBC) as part of routine bloodwork or other investigations [1]. In patients that are otherwise healthy, signs or symptoms may not be obvious even at low Hgb concentrations if the anemia develops slowly

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Table 30.1 General signs and symptoms of anemia

Symptoms	Signs
Fatigue	Pale skin or mucous membranes
Weakness	Tachycardia
Dizziness or lightheadedness	Palpitations
Headache	Shortness of breath on exertion

over time [4]. In anemias that develop very rapidly, symptoms tend to be more pronounced. Because hemoglobin delivers oxygen, signs and symptoms are often related to lack of oxygen delivery including fatigue, weakness, dizziness, or shortness of breath. Cardiac signs or symptoms may include chest pain, palpitations, or tachycardia. On examination, patients may exhibit pallor of skin and/or mucous membranes. In the elderly, signs and symptoms of anemia may overlap with other causes and include increased falls, reduced cognition, and overall physical decline [1]. Depending on the cause of the anemia, patients may have additional symptoms related to underlying nutritional deficiencies such as neurologic symptoms as a result of vitamin B12 deficiency. General signs and symptoms of anemia are summarized in Table 30.1.

Etiology

Anemia occurs when there is an imbalance in the production and destruction or loss of RBCs. There are three primary causes of anemia: blood loss, inadequate RBC production, and increased RBC destruction [4]. Blood loss can be caused by acute (e.g., trauma) or chronic (e.g., gastrointestinal ulcers) bleeding. Nutritional deficiencies (B12, folate, iron), chronic kidney disease, thyroid disease, liver disease, bone marrow failure, and anemia due to chronic disease or inflammation can lead to inadequate RBC production. Increased destruction of RBCs may be caused by hereditary (e.g., sickle cell anemia, thalassemia) or acquired (e.g., immune hemolytic anemia) conditions.

Approach to the Assessment of Anemia

Anemia reflects an underlying disease or condition; therefore, it is important to conduct a thorough work-up to determine the cause in order to guide appropriate management. Laboratory tests should be evaluated in the context of the patient history and physical examination to diagnose anemia. Laboratory tests also play an important role in assessing response to treatment.

History and Physical Examination

A detailed patient history may provide clues as to the cause of the anemia [1]. Specific questions to ask the patient may depend on the situation as well as laboratory tests that are available.

- *Signs of blood loss* – Consider blood loss from the gastrointestinal (GI) tract, genitourinary tract, or as a result of trauma. A menstrual history should be taken for women to rule out heavy menstrual bleeding.
- *Past medical history* – Chronic conditions associated with anemia include: rheumatoid arthritis, systemic lupus erythematosus, chronic kidney disease, congestive heart failure, liver disease, thyroid disease, hemolytic disorders, aplastic anemia, certain cancers (e.g., leukemia, lymphoma), infections (e.g., human immunodeficiency virus, tuberculosis, osteomyelitis), inflammatory bowel disease, celiac disease.
- *Surgeries or procedures* – Recent surgeries may cause anemia or result in secondary bleeding. Gastric bypass surgery can lead to reduced absorption of vitamins. A history of recent blood donation should also be considered.
- *Medications* – Drugs may cause or contribute to anemia through different mechanisms. For example, non-steroid anti-inflammatory drugs (NSAIDS), anticoagulants, and antiplatelet agents may promote bleeding and iron deficiency. Certain chemotherapy or antimalarial agents, zidovudine, trimethoprim,

Table 30.2 Common laboratory tests used to diagnose anemias

Test	Reference range[a]	Description
Complete blood count		
Red blood cells (RBCs)	(Males) 4.5–6.0 × 10^{12}/L (Females) 4.0–5.6 × 10^{12}/L	–
Hemoglobin (Hgb)	(Males) 137–180 g/L (Females) 120–160 g/L	Amount of hemoglobin in a unit of blood
Hematocrit (Hct)	(Males) 0.40–0.54 (Females) 0.36–0.48	Percentage volume of RBCs in the blood
Mean corpuscular volume (MCV)	82–100 fL	Size of the average RBC
Mean corpuscular hemoglobin concentration (MCHC)	320–360 g/L	Average concentration of Hgb in the RBC
Red cell distribution width (RDW)	11–16%	Measures variation in RBC volume
Iron studies		
Serum iron	(Males) 8–30 µmol/L (Females) 6–28 µmol/L	Measures iron bound to transferrin
Total iron binding capacity (TIBC)	40–80 µmol/L	Measures iron binding capacity of transferrin
Transferrin saturation index	0.15–0.50	Ratio of serum iron to TIBC expressed as a percent
Ferritin	(Males) 30–400 µg/L (Females) 13–375 µg/L	Indicator of iron body stores. Caution interpreting ferritin in the presence of inflammatory conditions or malignancy
Others		
Vitamin B12	155–700 pmol/L	–
Folate – Serum	>12.0 nmol/L	–
Reticulocyte count	40–100 × 10^{9}/L	Immature RBCs

[a]Example adult reference ranges obtained from Calgary Laboratory Services. Accessed May 29, 2018. Available at http://www.calgarylabservices.com/lab-services-guide/lab-tests/

sulfasalazine, phenytoin, phenobarbital, metformin, and proton pump inhibitors may cause macrocytic anemias. Ribavirin, and less commonly select antibiotics, NSAIDS, and other agents can cause hemolytic anemia.

- *Diet* – Dietary history may suggest possible deficiencies such as B12, folate, or iron in the diet.
- *Family history* – This may be useful to identify potential inherited anemias, such as thalassemia or sickle cell disease.
- *Pregnancy* – Women that are pregnant have increased iron demands and are at a higher risk of iron deficiency anemia.

In addition to general signs of anemia on physical examination, there may be additional findings that are suggestive of specific causes [1]. For example, jaundice or scleral icterus may be a sign of hemolytic anemia. Patients with B12 deficiency may experience altered mental status or numbness and tingling in their hands and feet. Iron deficiency anemia can cause brittle nails and a smooth or swollen tongue.

Laboratory Tests

Common laboratory tests used for diagnosis of anemias include the complete blood count (CBC), reticulocyte count, iron studies, and vitamin B12 and folate levels [1]. A summary of these laboratory tests and what they measure is found in Table 30.2. Decreased Hgb or RBC count confirms that the patient has anemia. However, it is important to recognize that Hgb and Hct may decrease when plasma volume increases (fluid overload) and may increase when plasma volume decreases (dehydration) [5]. Evaluating trends in Hgb (chronic versus more recent onset) as well as absolute values in the context of the patient history can provide useful information.

The next step is to look at mean corpuscular volume (MCV) in order to categorize the anemia

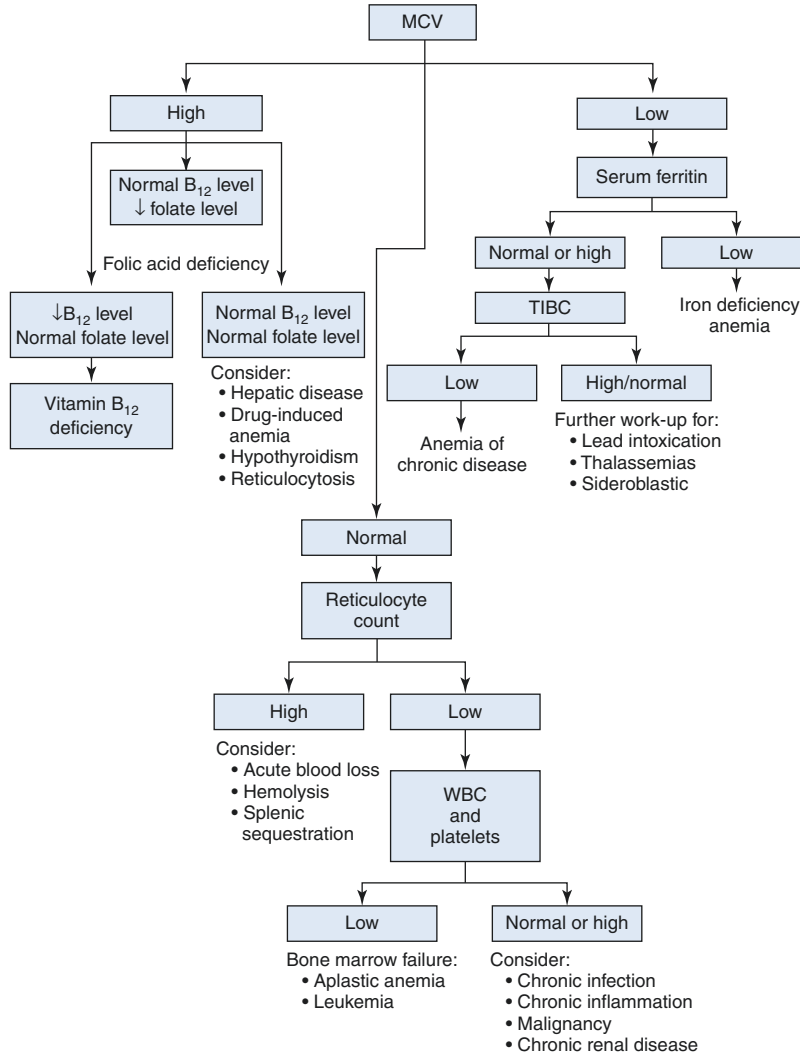


Fig. 30.1 General algorithm for diagnosis of anemias. Reprinted by permission from McGraw-Hill Education. BJ Wells, JT DiPiro, TL Schwinghammer, CV Dipiro. *Pharmacotherapy Handbook*, Tenth Edition

and narrow down potential causes. An algorithm for assessing anemia based on MCV is found in Fig. 30.1. Anemias are commonly classified as microcytic (MCV < 82 fL), macrocytic (MCV > 100 fL), or normocytic (MCV 82–100 fL). MCV represents a measurement of the average size of RBCs, and therefore can sometimes be misleading in patients with mixed anemias. For example, MCV may appear normal in patients who have both anemia of chronic disease and iron deficiency anemia. In some cases, the red cell distribution width (RDW) may provide additional information. A normal RDW indicates homogeneity in RBC size, whereas an increased RDW indicates variation in RBC size. A peripheral smear may be ordered to examine the size and shape of RBCs as well as abnormal circulating cells [1].

In patients with microcytic anemia, iron studies are needed to differentiate the cause. A low serum ferritin is usually the best indicator of iron deficiency anemia. Because serum ferritin reflects iron stores in the body, ferritin decreases even before the anemia develops [5]. However, ferritin is an acute-phase protein and is therefore elevated by inflammation. In this situation, a ferritin level greater than 100 μg/L suggests iron deficiency is unlikely [5]. Other iron studies, including serum iron, total iron binding capacity (TIBC), and transferrin saturation are often not that helpful in

Table 30.3 Laboratory differentiation of iron deficiency anemia (IDA) and anemia of chronic disease (ACD)

Test	IDA	ACD	IDA + ACD
Mean corpuscular volume (MCV)	↓	Normal or ↓	Normal or ↓
Red cell distribution width (RDW)	↑	Normal	↑
Serum iron	↓	↓	↓
Total iron binding capacity (TIBC)	↑	Normal or ↓	Normal or ↓
Transferrin saturation	↓	Normal or ↓	↓
Ferritin	↓	Normal	Normal

distinguishing iron deficiency anemia from anemia of chronic disease [5]. A trial of iron therapy may be necessary to confirm the diagnosis. RDW is often increased in iron deficiency anemia as smaller microcytic cells are formed. Table 30.3 compares laboratory test results in patients with iron deficiency anemia and anemia of chronic disease.

Normocytic anemia can have a number of different causes and further investigations are often needed [1]. The reticulocyte count can be useful in differentiating potential causes of normocytic anemia. A high reticulocyte count suggests the bone marrow is functioning appropriately in response to the anemia and thus potential causes may include acute blood loss or hemolysis. In the case where hemolytic anemia is suspected, additional useful tests may include lactate dehydrogenase, haptoglobin, or a Coombs test [1]. In patients with a normocytic anemia and a low reticulocyte count, potential causes may include bone marrow failure or chronic infection, inflammation, malignancy or chronic kidney disease. Evaluation of other blood cells (white blood cells and platelets), serum creatinine, liver tests as well as consideration of the patient's history and physical examination will aid in narrowing down the cause.

Assessing macrocytic anemias should include reviewing medications that the patient is taking, as well as any history of alcohol use to determine whether these may be implicated in causing the anemia [1]. Zidovudine, chemotherapy drugs, and hydroxyurea are common causes of macrocytic anemia. To rule out nutritional deficiencies, vitamin B12 and serum folate levels should be ordered. Low serum folate levels suggest folate deficiency; however, it is important to note that serum folate levels are relatively nonspecific and can change rapidly with dietary restriction [1]. Dietary deficiency of folate is generally uncommon as a result of foods fortified with folic acid in many countries, however decreased absorption of folate or increased demands (e.g., pregnancy) can result in deficiency. Deficiency in vitamin B12 is caused by low dietary intake or more frequently, poor absorption. A falsely low B12 level may be seen during pregnancy and in women taking oral contraceptives [1]. A vitamin B12 level <150 pmol/L is suggestive of deficiency. However, vitamin B12 levels at the lower end of the reference range may be associated with clinical symptoms of B12 deficiency and would therefore require treatment.

Management and Follow-Up Assessment

Management of the anemia depends on the cause as well as the patient's clinical status. For example, in anemia of chronic disease, the anemia is often corrected by treating the underlying disease. Specific treatment of the various types of anemia is beyond the scope of this chapter. However, treatment and follow-up assessment of iron, folic acid, and vitamin B12 deficiency are briefly summarized below.

Once the diagnosis of iron deficiency anemia and the underlying cause has been determined, treatment is often initiated with oral iron supplements. Patients may be encouraged to increase dietary intake of foods rich in heme iron (e.g., lean red meats, fish) or non-heme iron (e.g., legumes, tofu) [6, 7]. Ascorbic acid (vitamin C) increases absorption of non-heme iron, whereas tannins found in tea and coffee can decrease absorption. For oral iron supplements, the usual target dose is 100–200 mg of elemental iron per day in divided doses [6]. Common iron supplements as well as their elemental iron content are summarized in Table 30.4 [6]. For maximum absorption, oral iron should be

Table 30.4 Comparison of oral iron supplements

Iron supplement	Elemental iron	Usual maximum dose (adults)
Ferrous gluconate 300 mg tablet	35 mg	Two tablets three times daily
Ferrous sulfate 300 mg tablet	60 mg	One tablet three times daily
Ferrous fumarate 300 mg tablet	100 mg	One tablet two times daily
Heme-iron polypeptide (e.g., Proferrin®) 11 mg tablet	11 mg as heme iron	One tablet three times daily
Polysaccharide-iron complex (e.g., Feramax®) 150 mg capsule	150 mg	One capsule once daily

administered on an empty stomach, 1 h before or 2 h after a meal. Administration of oral iron supplements with a glass of orange juice can improve absorption. Side effects commonly encountered with oral iron supplements are abdominal pain, nausea, constipation, diarrhea, metallic taste, and dark stools [6]. If patients are having difficulty tolerating oral iron, management strategies may include starting with a lower dose of elemental iron and titrating slowly, switching to a preparation with a lower amount of elemental iron, or administering iron with small snacks or meals. There are a number of drug-drug interactions with iron supplements to be aware of including antacids, proton pump inhibitors, H2-antagonists, and tetracycline or doxycycline that can decrease iron absorption. In addition, iron can impact the absorption of levodopa, levothyroxine, fluoroquinolones, bisphosphonates, integrase strand transfer inhibitors, tetracycline, and doxycycline; therefore, administration times should be separated [8]. To assess response to treatment, a CBC should be ordered approximately 4 weeks after starting therapy [6, 7]. Hgb is expected to increase >10 g/L after 4 weeks of treatment [6]. Iron deficiency anemia usually corrects within 2–4 months of starting therapy if appropriate doses are used and the underlying cause is corrected. However, oral iron is recommended to be continued for about 3 months after Hgb normalizes in order to replenish iron stores. A serum ferritin should be ordered to confirm repletion of iron stores prior to discontinuing therapy.

Folate deficiency is treated with folic acid supplementation. The dose of folic acid used and duration depends on the cause of the deficiency; however, common doses for treatment are 1–5 mg orally per day [9]. Recommended intake of folic acid in adults through diet and supplements is 400 μg/day. The United States Preventive Services Task Force recommends women planning or capable of pregnancy take a daily supplement of 400–800 μg/day [10]. Foods that are rich in folic acid include green leafy vegetables, citrus fruits, and grains. It is important that vitamin B12 deficiency is ruled out prior to starting folic acid, as folate may correct the anemia but does not treat the neurologic manifestations of vitamin B12. CBC should be repeated at approximately 1 month to assess response to treatment. Usually, Hgb normalizes within 2 months. Folate level should be repeated in approximately 3–4 months.

B12 deficiency can be treated with oral or parenteral vitamin B12 [9]. The decision to use oral versus parenteral initially may depend on the cause of the anemia (e.g., malabsorption), the severity, and presence of neurologic symptoms. High dose oral vitamin B12 (1–2 mg/day) has been shown to be as effective as intramuscular administration in terms of correcting the anemia and neurologic symptoms [11]. However, parenteral vitamin B12 may be preferred until B12 levels are corrected in those with neurologic symptoms as well as patients who are nonadherent to oral B12 therapy. There are a number of dosing schedules for parenteral vitamin B12 [12]. For patients with dietary deficiency, lower doses of vitamin B12 can be used (e.g., 250 μg/day) [12]. Patients with pernicious anemia or any B12 deficiency caused by malabsorption require lifelong therapy [9]. CBC and vitamin B12 level should be repeated 1–2 months after initiation of therapy to ensure correction.

Clinical Pearls

- Investigation of the underlying cause of the anemia is necessary.
- MCV categorizes anemia into microcytic, normocytic, and macrocytic.
- In mixed anemias, MCV may be misleading – assessing MCV along with RDW (and/or the peripheral smear) may be helpful to identify mixed anemias.
- Reticulocytes can help categorize anemias as hypo- or hyper-proliferative.
- Pharmacists play an important role in assessing patients with anemia and monitoring response to treatment.

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