Chapter 4

Autonomic Agents

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Learning Objectives

- Identify current pharmacologic agents that are appropriate for each condition/diagnosis.
- Recommend optimal pharmacologic interventions based on patient-specific characteristics.
- Provide appropriate patient-specific counseling points and optimal overall medication management.

Key Terms: parasympathetic (cholinergic) agents, anticholinergic agents, antiparkinsonian agents, antimuscarinics/antispasmodics, sympathomimetic (adrenergic) agents, alpha-adrenergic agonists, beta-adrenergic agonists, non-selective beta-adrenergic agonists, selective beta-adrenergic agonists, alpha- and beta-adrenergic agonists, sympatholytic (adrenergic blocking) agents, alpha-adrenergic blocking agents, nonselective alpha-adrenergic blocking agents, selective alpha-adrenergic blocking agents, beta-adrenergic blocking agents, nonselective beta-adrenergic blocking agents, selective beta-adrenergic blocking agents, skeletal muscle relaxants, centrally acting skeletal muscle relaxants, direct-acting skeletal muscle relaxants, GABA derivative skeletal muscle relaxants, neuromuscular blocking agents, skeletal muscle relaxants miscellaneous agents, autonomic miscellaneous agents

Overview of Autonomic Agents

The variety of vital functions that are regulated by the nervous system has led to the development of a class of drugs with a significant number of important therapeutic uses. The central nervous system is divided into two distinct pathways based on the presence of parasympathetic (cholinergic/muscarinic) versus sympathetic (adrenergic) receptors. Autonomic drugs generally produce either excitation or inhibition of certain types of smooth muscle, such as those found in the blood vessels of organs and glands and in the skin and mucous membranes. These drugs may also lead to metabolic and endocrine changes that include, but are not limited to, increased hepatic glycogenolysis and modulation of the secretion of insulin and other hormones. Respiration, gastrointestinal motility, and muscular movements are also influenced by drugs that impact the autonomic system.

Many of the agents within the autonomic drug class have either little or no action when administered orally, and the degree of their action and the intensity of their pharmacologic effects vary significantly when the drugs are administered intramuscularly, intravenously, or are inhaled into the lungs. The response to autonomic agents depends on the density and proportion of receptors available, but is also balanced by the body's reaction to reflex homeostatic adjustments coordinated by the baroreceptor system. Clinicians must be mindful that patients with comorbid medical illness or advancing age will exhibit altered reaction and reflex mechanisms and, therefore, may be subject to exaggerated or unexpected adverse drug reactions or impaired intended therapeutic effects of autonomic drugs.

Autonomic drugs are used for a number of indications that include blood pressure reduction, respiratory bronchodilation, and allergic reactions/anaphylaxis. Autonomic agents are frequently selected for use in patients experiencing cardiac arrest and who are in need of cardiopulmonary resuscitation. In addition, they are routinely used in topical form for vasoconstriction and to shrink mucous membranes. Interest in the use of these agents for patients with congestive heart failure has been increasing, and although the responses of certain receptors are often less robust in a failing heart, there may be future consideration for new roles for agents within this class.

4.1 Autonomic-Parasympathomimetic (Cholinergic) Agents

Drugs within this therapeutic category are agents that imitate or influence the action of the neurotransmitter acetylcholine. Muscarinic acetylcholine receptors in the peripheral nervous system are found with the highest density within the central nervous system (CNS), the hippocampus, cortex, and thalamus. Acetylcholine (ACh) is the neurotransmitter responsible for stimulating muscarinic receptors; thus it is described as having "cholinergic" activity. Acetylcholine is the primary neurotransmitter of nerve signals within the peripheral nervous system and it is quickly broken down by the enzymes acetylcholinesterase (AChE) and plasma butyrylcholinesterase, rendering it inactive. Drugs that mimic muscarinic agonists are generally able to provide longer actions systemically owing to chemical manipulations involving congeners (relative "like" substances) of ACh or natural alkaloids that stimulate both nicotinic and muscarinic receptors. The action of ACh is highly variable, but can be generally described as activity influencing parasympathetic nerves in the sweat glands, skeletal muscle with somatic innervation, and smooth muscle in blood vessels and other cardiac tissue. Dilation of blood vessels, increased bodily secretions, and decreased heart rate are all associated with the actions of acetylcholine and are responsible for the adverse-effect profile, as well as the beneficial therapeutic effects, of a drug within this therapeutic category.

The properties of muscarinic receptors vary. Five such receptors have been identified, designated as M1 through M5. Although specific muscarinic receptor subtypes have been identified, the development of selective agonists and antagonists for these subtypes has been a challenge because currently recognized agents have a broad spectrum of activity at most of these receptors.

Drugs influencing ACh are responsible for respiratory bronchoconstriction and secretion as well as urinary effects, with their stimulating actions causing detrusor muscle contraction, increased voiding pressure, and ureteral peristalsis. Gastrointestinal (GI) actions that result from exposure to ACh include, but are not limited to, increased secretions. For this reason, caution should be used when considering the use of these agents in patients with peptic ulcer disease, as acetylcholinesterase inhibitors can increase stomach acid.

Both the bladder and GI effects are thought to be mediated by multiple muscarinic receptor subtypes. ACh stimulates secretions from other glands, including the lacrimal, nasopharyngeal, salivary, and sweat glands. Endogenous and exogenous ACh has limited ability to cross the blood–brain barrier; however, muscarinic agonists that are formulated to enter into the CNS play an important role in cognitive function, motor control, appetite regulation, nociception, seizure threshold, and other processes.

Due to their intrinsic pharmacologic actions, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and atrioventricular (AV) block, which may then exacerbate syncope or hypotensive events. All patients should be considered at risk for adverse cardiac effects when they take cholinesterase inhibitors, as bradycardia and heart block have occurred in patients without previously diagnosed cardiac conduction abnormalities. These agents should be used with caution in patients with cardiac disease, such as sick sinus syndrome, severe cardiac arrhythmias, or cardiac conduction disturbances (e.g., sinoatrial block, AV block).

Acetylcholinesterase inhibitors are also likely to exaggerate the effects of neuromuscular blocking agents during anesthesia, resulting in potentially extended respiratory depression. Among other concerns, their use is not recommended in patients recovering from gastrointestinal surgery due to the effects on the GI tract resulting from the cholinergic actions of these drugs.

Autonomic-Parasympathomimetic (Cholinergic) Agents

Ambenonium
Bethanechol
Cevimeline
Donepezil

Galantamine
Neostigmine
Physostigmine
Pyridostigmine
Rivastigmine

Case Studies and Conclusions

BP is a 72-year-old female with newly diagnosed mild-stage Alzheimer's disease (AD). Her daughter LS would like to know which of the acetylcholinesterase inhibitors her mother could take for the duration of her illness as it progresses.

1. Which agent is approved only for mild to moderate illness, but NOT severe illness?

   a. Donepezil
   b. Galantamine
   c. Rivastigmine
   d. Pyridostigmine

Answer B is correct. Of the three acetylcholinesterase inhibitors, only galantamine is approved only for mild to moderate illness, not for severe stages of AD.

LS would like to know more about the possible side effects of these acetylcholinesterase inhibitors.

2. What is the most common side effect that she should expect her mother to experience?

   a. Weight gain
   b. Tachycardia
   c. Seizure
   d. Diarrhea

Answer D is correct. Diarrhea is the most common side effect of acetylcholinesterase inhibitors among the options listed.

JR is a candidate for bethanechol therapy due to a recent diagnosis of neurogenic bladder.

1. Which concurrent medical illness would preclude use of bethanechol due to an absolute contraindication?

   a. COPD
   b. Hypertension
   c. Inflammatory bowel disease
   d. Orthostatic hypotension

Answer C is correct. Inflammatory bowel disease (especially severe conditions) is a contraindication to bethanechol use. The other conditions warrant caution, but do not present as potentially serious a concern (i.e., patients should avoid their use "if possible").

JR has read about this new medication and is worried about the potential for nausea and stomach upset.

2. What is a recommendation to reduce the potential for this adverse effect?

   a. Administer on an empty stomach 1 hour before a meal
   b. Administer on a full stomach 2 hours after a meal
   c. Administer without regard to meals, take just before bedtime
   d. Administer without regard to meals, take just upon awakening

Answer A is correct. Timing administration of bethanechol for 1 hour before a meal provides the necessary "empty stomach" condition to optimize this therapy and to reduce adverse GI side effects.

4.2 Autonomic-Anticholinergic Agents

The muscarinic receptor antagonists include natural, synthetic, and semisynthetic alkaloid derivatives. The antagonists that have been developed to mimic the action of the natural compounds exhibit greater selectivity (though not absolute) as well as different rates of onset and durations of action (some shorter, some longer). Muscarinic antagonists inhibit the action of ACh by preventing binding to parasympathetic and sympathetic cholinergic receptors. For this reason, this class of medications has been termed "anticholinergic" agents.

Decreased salivary and bronchial secretions and sweating, pupillary dilation, visual changes, increased heart rate, bronchodilation, inhibited urination, and decreased intestinal tone and motility are all typical effects seen with the administration of anticholinergic medications. Some antagonists of acetylcholine, such as trihexyphenidyl, exhibit additional inhibition of cholinergic stimuli at muscarinic receptors in the CNS and, to a lesser extent, in smooth muscle. This multiple receptor site action allows for additional direct antispasmodic actions on smooth muscle, as well as the typical antisecretory, mydriatic, and positive chronotropic activities seen with these agents.

Autonomic-anticholinergic agents have been used to reduce GI hypermotility. However, caution must be exercised when they are used in patients with gastroesophageal reflux disease (GERD) or hiatal hernia associated with reflux esophagitis, because the decreased gastric motility and relaxation of the lower esophageal sphincter can promote gastric retention and aggravate reflux in these patients. The anticholinergic effects of drugs in this class can also cause increased intraocular pressure, so they should be used with extreme caution in patients with open-angle glaucoma. Their use may cause patients to complain of dry eyes and discomfort when using contact lenses, often requiring additional lubricating drops or leading to discontinuation of the use of lenses while on these medications. Older male patients may exhibit exacerbations of symptoms of benign prostatic hypertrophy due to worsening urinary retention. Anticholinergic drugs may exacerbate symptoms associated with dementia and may cause tachycardia, increasing adverse risks for patients with cardiac disease. The total anticholinergic side effect burden increases when multiple concurrent medications with the same side effects are co-administered and can lead to increased toxicity.

While receptor selectivity has been difficult to target, some synthetic and semisynthetic muscarinic receptor antagonist derivatives have exhibited a greater degree of selectivity for subtypes of muscarinic receptors. Examples of such agents include homatropine and tropicamide, which both have a shorter duration of action than atropine, and methscopolamine, ipratropium, and tiotropium, which do not readily cross the blood–brain barrier or other membranes. The synthetic derivatives possessing some degree of M3 receptor selectivity include the newer agents darifenacin and solifenacin.

Antiparkinsonian Agents

Benztropine (*see also the Antiparkinsonian Agents in the Central Nervous System chapter*)
Diphenhydramine (*see also the First-Generation Antihistamines section in the Antihistamines chapter*)
Procyclidine (*see also the Central Nervous System chapter*)
Trihexyphenidyl (*see also the Antiparkinsonian Agents in the Central Nervous System chapter*)

Antimuscarinics/Antispasmodics

Like other anticholinergic medications, antimuscarinic agents can cause blurred vision, drowsiness, or dizziness. For this reason, patients should use caution when driving or operating machinery until they determine the side effects of the drug. Due to the potential to increase heart rate and to potentiate arrhythmias, some patients may experience ischemia when using these agents. Antimuscarinic agents should be used with caution in patients with known cardiac disease or in other comorbid disease states that could be worsened with tachycardia.

Antimuscarinics should be used with caution in patients with renal impairment or renal failure because both their metabolites and the unchanged parent drug are excreted in the kidneys, leading to an unwelcomed increase in anticholinergic effects. Additionally, the antimuscarinic actions of atropine may cause urinary retention and should be avoided in patients with prostatic hypertrophy and urinary or bladder obstruction.

Short-acting antimuscarinic antagonists (SAMAs) have generally been used along with short-acting β_2 agonists (SABAs) as the backbone of therapy for a number of respiratory illnesses, including chronic obstructive pulmonary disease (COPD). Although COPD and asthma are different inflammatory processes that produce different kinds

of bronchoconstriction, both diseases can have serious consequences if not managed adequately. COPD appears to involve a significant cholinergic component, so antimuscarinics can be as effective in inhibiting bronchoconstriction as SABAs are at reversing it.

Antimuscarinic agents have also been used as augmentation therapy in treatment of irritable bowel disease and peptic ulcer disease. However, their adverse effects limit their use and only a limited number of well-controlled studies have been published to support their use in most conditions. Consequently, these agents have been replaced by other medications that are more effective or cause fewer adverse effects. A careful review of individual agents listed on the companion drug grid is warranted for a more comprehensive understanding of the unique characteristics of each drug and will help you to prepare to answer the case studies at the end of each section.

Antimuscarinics/Antispasmodics

Aclidinium
Atropine
Belladonna
Dicyclomine
Glycopyrrolate
Hyoscyamine
Ipratropium
Mepenzolate
Methscopolamine
Propantheline
Scopolamine
Tiotropium
Umeclidinium

Case Studies and Conclusions

JP is a 55-year-old college professor who has been a 2-pack-per-day smoker for the last 20 years. He presents to the clinic today with a new diagnosis of COPD and a prescription for tiotropium capsule inhalation (Spiriva Handihaler). He is also seeking information on smoking cessation. JP has no other medical comorbidities, but his primary care provider stated that his renal function is "lower" than she would like it to be.

1. Which adverse effects from tiotropium might JP experience in light of his impaired renal function as compared to his peers with normal/adequate renal function?

   a. Renal failure
   b. Increased anticholinergic effects
   c. Elevated liver function tests (LFTs)
   d. syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Answer B is correct. Tiotropium is primarily eliminated in the urine, so patients with moderate to severe renal impairment (creatinine clearance [CrCl] less than 60 mL per minute) may be at an increased risk of anticholinergic-induced events.

One month after initiating tiotropium therapy, JP returns to clinic and describes having used this medication to control one of his "breathing attacks," only to have his family call 911 because he was unable to catch his breath. He denies any swelling of his lips or tongue during the events.

2. What would be the most reasonable approach in discussing future recommendations for JP so that he can have more successful treatment and symptom control in the future?

   a. Discontinue tiotropium, because he must be allergic to it.
   b. The lactose in tiotropium causes this reaction in everyone.
   c. Tiotropium is not intended to be a rescue intervention.
   d. Seek a diagnostic reevaluation.

Answer C is correct. Tiotropium is not intended for rescue therapy of acute bronchospasm attacks. Although immediate hypersensitivity reactions (including swelling of the lips, tongue, or throat) may occur after its administration, JP has been taking his tiotropium only "as needed," which is likely the reason for his shortness of breath.

JP describes a "less robust" improvement in his COPD than he expected with the start of tiotropium a month ago.

3. What do you advise?

a. Tiotropium may take up to 8 weeks to see the full effect.
b. He must be using the product incorrectly.
c. His COPD may be too severe for this medication to be effective.
d. He may be a candidate for a lung transplant.

Answer A is correct. Tiotropium may take up to 8 weeks to see the full effect. Given that this patient has been having "some relief," though not as "robust" as he would expect, continuation would be warranted to see if he can achieve his optimal therapeutic goals.

CS is a 25-year-old waitress who is experiencing irritable bowel disease. She has received a prescription for dicyclomine 10 mg capsules to be taken 4 times daily for 30 days. She has not begun taking her medication yet and asks you if you have any "recommendations" for her as a clinician.

1. What would you advise CS regarding her new medication?

a. This type of medication takes time to build up in her system before it works.
b. She should request an increased dose after a few days if the medication does not work.
c. She should expect immediate results with complete symptom resolution.
d. Data indicate that this medication works best if used longer than 2 weeks.

Answer B is correct. This is a relatively low dose, and the manufacturer recommends an increase in dose up to 40 mg PO 4 times per day during the first week to control symptoms. If the dosage is not effective within 2 weeks of therapy, or if side effects develop that require doses less than 80 mg per day PO, the manufacturer recommends drug discontinuation.

CS tells you that the pharmacist indicated that this drug carries a universal prescribing alert relative to its anticholinergic side effects.

2. What would you describe as one of the elements of this universal prescribing alert?

a. This class of medications may decrease the effectiveness of birth control pills.
b. This class of medications may cause ovarian benign hyperplasia.
c. This class of medications may cause wakefulness and insomnia.
d. This class of medications may alter her ability to regulate her body temperature.

Answer D is correct. Anticholinergic medications impair the body's natural ability to sweat and decrease an elevated body temperature. Generally, these agents are sedating. They also cause complications for male patients who are predisposed to benign prostatic hypertrophy. They are not known to interfere with the efficacy of oral contraceptives.

4.3 Autonomic-Sympathomimetic Adrenergic Agents

Sympathomimetic amines are adrenergic receptor agonists that produce sympathomimetic-stimulant-like effects that facilitate the release, block the transport (or reuptake), decrease metabolism or "imitate" the actions of norepinephrine (NE), a hormone that is associated with sympathetic neurons. Some medications (such as ephedrine) may directly activate the release of NE while also indirectly causing a release of NE; thus, they are classified as "mixed-acting" sympathomimetic drugs. Other agents are described as either direct or indirect acting. These agents can be used to treat cardiac arrest and low blood pressure among other conditions.

While autonomic-sympathomimetic agents are indicated for use in patients with open-angle glaucoma, they can exacerbate closed-angle glaucoma and, therefore, are contraindicated in patients with this condition. Other contraindications include severe hypertension and ventricular tachycardia, including arrhythmias associated with

tachycardia. These agents are also contraindicated in patients with thyrotoxicosis, including hyperthyroidism. The FDA labeling of autonomic-sympathomimetic agents carry black box warnings with which clinicians should become familiar.

Autonomic-sympathomimetic agents, particularly when administered parenterally, should be avoided in patients with severe cardiac disease (such as coronary artery disease, angina, and myocardial infarction) or with bradycardia or AV block. Further caution is warranted in patients with uncontrolled hypertension due to the increased likelihood of adverse cardiac events. Even ophthalmic or nasal formulations can complicate these preexisting conditions, so they should also be used with caution in patients with known or suspected cardiac disease. This caution is extended to patients with cerebrovascular disease and history of or increased risk for stroke. Severe tissue necrosis due to vasoconstriction of small blood vessels has been reported with autonomic-sympathomimetic agents, so caution in patients with extensive peripheral vascular disease is warranted to avoid excessive vasoconstriction or ischemia of vital organs.

These agents should also be used with caution in men with symptomatic, benign prostatic hypertrophy, due to the potential for urinary retention. Sympathomimetic autonomic agents may also stimulate insulin production, increase glycogenolysis in the liver, and complicate the management of diabetes mellitus.

Alpha-Adrenergic Agonists

Midodrine
Phenylephrine
Clonidine (*see also the Hypotensive Agents section in the Cardiovascular Agents chapter*)
Guanabenz (*see also the Hypotensive Agents section in the Cardiovascular Agents chapter*)
Methyldopa (*see also the Hypotensive Agents section in the Cardiovascular Agents chapter*)

Beta-Adrenergic Agonists

Beta-adrenergic drugs may exhibit a strong inotropic effect that alters or changes the strength of muscular contraction of the heart and, therefore, are potentially harmful in the presence of a severe mechanical obstruction such as idiopathic hypertrophic subaortic stenosis. In patients with this condition, the presence of narrow aortic valves increases the demand on the left ventricle to pump harder in order to force blood through these valves, resulting in enlargement of the left ventricle, contributing to increased risk of heart failure. Certain medications in this category can be used with caution to treat patients with cardiac diseases including acute myocardial infarction, unstable angina, and severe coronary artery disease. The inotropic and chronotropic effects of drugs within this class may increase cardiac oxygen demand due to the increased muscle activity.

Use these agents with caution in patients with occlusive vascular disease such as atherosclerosis, peripheral vascular disease, or Raynaud's disease, as well as in patients with preexisting vascular damage because of the risk of vasoconstriction and subsequently decreased circulation to the extremities associated with some of these drugs (such as dopamine).

Nonselective Beta-Adrenergic Agonists

Isoproterenol

Selective Beta$_1$-Adrenergic Agonists

Dobutamine
Dopamine

Selective Beta$_2$-Adrenergic Agonists

These medications are further subdivided into short-acting and long-acting beta$_2$ receptor agonists (SABA and LABA), which are generally administered by oral inhalation via metered-dose inhaler (MDI) or nebulizer for patients with a variety of respiratory conditions. The LABAs are indicated for maintenance treatment, whereas SABAs may be used for rescue therapy if the patient experiences breakthrough shortness of breath. All LABAs are contraindicated for monotherapy treatment of asthma. Thus, if LABAs are prescribed for patients with asthma, they must be used concurrently with a medication indicated for use to control asthma (i.e., inhaled corticosteroid [ICS]).

Some of these agents (including certain LABAs) can be used to prevent exercise-induced bronchospasm (EIB). When used for EIB, the dose should be administered at least 15 minutes before exercise, with additional doses taken only according to the manufacturer's directions and not in excess of the Food and Drug Administration's (FDA) total daily recommended maximum dose. Patients who are on scheduled SABA/LABA maintenance therapy should not use additional doses to prevent EIB. If maintenance dosing or dosing prior to exercise with SABA/LABA therapy does not control EIB, then other appropriate treatment for EIB should be considered; this would include avoiding the use of LABAs alone without another long-acting controller medication because of the increased rate of serious adverse events such as asthma-related mortality, exacerbations requiring hospitalization, increased costs, and morbidity. Controller agents generally used concurrently with LABAs include ICSs, which are typically added as first-line adjuncts to SABAs; however, exact guidance regarding the addition of a LABA to the EIB treatment regimen is not available.

Inhaled formulations are preferred over oral (swallowed) bronchodilators for many respiratory conditions, including COPD. Given that many of these products are administered via oral inhalation, it is important that clinicians provide education on proper technique to optimize the drug therapy.

Selective Beta$_2$-Adrenergic Agonists

Albuterol/levalbuterol
Arformoterol
Formoterol
Indacaterol
Metaproterenol
Olodaterol
Salmeterol
Terbutaline
Vilanterol

Alpha-and Beta-Adrenergic Agonists

These agents are well known for their vasoconstricting properties. From a therapeutic standpoint, this effect may be beneficial in decreasing anaphylaxis as well as when used for an intervention for hypotension and shock. The class-related side effects are mainly attributable to this vasoconstriction. Caution should be observed to avoid extravasation during intravenous administration, as peripheral ischemia, tissue necrosis, and gangrene in the surrounding area can occur due to vasoconstriction. These agents must also be used with caution in patients with cardiovascular disease, diabetes, prostatic hyperplasia, seizures, thyroid dysfunction, and unstable motor symptoms due to their cardiovascular effects.

Alpha-and Beta-Adrenergic Agonists

Droxidopa
Ephedrine
Epinephrine
Norephinephrine
Pseudoephedrine

Case Studies and Conclusions

SD is a 25-year-old male who has recently been diagnosed with asthma and has read that he should not be receiving a "LABA." He would like to discuss this issue further with his primary care provider.

1. What would you advise him?

   a. LABAs are appropriate to use when combined with corticosteroids.
   b. LABAs used as monotherapy are dangerous only if you overuse them.
   c. LABAs can be replaced with a once-daily SABA if the patient prefers.
   d. LABA monotherapy is dangerous only if the patient has severe asthma.

Answer A is correct. LABAs are appropriate when used in combination with other asthma control agents. Monotherapy with LABAs presents safety risks across the spectrum of care, not just when overused and not only in cases of severe asthma.

SABAs cannot be interchanged with LABAs on the same schedule. SABAs are short acting, so they need more frequent dosing than LABAs.

2. Which of the following medications would be considered a "LABA"?

   a. Albuterol
   b. Metaproteronol
   c. Salmeterol
   d. Isoproterenol

Answer C is correct. The rest of the options are SABAs.

DP is a 30-year-old female patient who would like to try to use a LABA for exercise-induced bronchospasm prior to dance class. She has a friend who uses formoterol for his asthma.

1. What would you advise this patient relative to her request?

   a. LABAs are not appropriate for EIB under any condition.
   b. Use formoterol 15 minutes prior to exercise.
   c. Add formoterol for EIB as an extra dose to the twice-daily scheduled dose.
   d. Use LABA intervention only if EIB occurs, not as prevention.

Answer B is correct. The formoterol package insert (PI) specifically recommends use prior to EIB, but the dose should not be "added" to the regular scheduled dose (it should not exceed the maximum daily dose [MDD]). Formoterol has an EIB indication, so not all LABAs are considered "inappropriate" for use in preventing bronchospasm; using any LABA as rescue, however, is inappropriate and dangerous.

DP has metabolic syndrome that results in abnormally high lipids, elevated blood glucose (she has diabetes), and obesity.

2. Which of these metabolic panels could be complicated by the use of LABAs such as formoterol?

   a. Hyperlipidemia
   b. Hyperglycemia
   c. Obesity
   d. All of these elements

Answer B is correct. LABAs and beta$_2$-adrenergic agonists as a class can cause an increase in blood glucose. The other answers are not associated with the use of LABAs.

4.4 Autonomic-Sympatholytic (Adrenergic Blocking) Agents

Autonomic-sympatholytic agents are associated with cardiac-stimulating effects, which in turn increase myocardial oxygen demand. Reflex tachycardia can be expected with their use and may exacerbate angina. For this reason, these agents are contraindicated in patients with acute myocardial infarction, a history of myocardial infarction, coronary insufficiency, angina, or any evidence of coronary artery disease.

Some drugs within this class may also have histamine-like effects and can stimulate gastric acid secretion, thereby complicating peptic ulcer disease.

Alpha Adrenergic Blocking Agents

Nonselective Alpha-Adrenergic Blocking Agents

Dihydroergotamine
Ergoloid mesylates
Ergotamine
Phenoxybenzamine
Phentolamine

Nonselective Alpha$_1$-Adrenergic Blocking Agents

Doxazosin (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Prazosin (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Terazosin (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)

Selective Alpha$_1$-Adrenergic Blocking Agents

Alfuzosin
Silodosin
Tamsulosin
Carvedilol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Labetalol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)

Beta-Adrenergic Blocking Agents

Nonselective Beta-Adrenergic Blocking Agents

Carvedilol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Labetalol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Nebivolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Pindolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Propranolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Stalol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Timolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)

Selective Beta-Adrenergic Blocking Agents

Acebutolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Atenolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Betaxolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Bisoprolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Esmolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)
Metoprolol (*see also the Adrenergic Agents section in the Cardiovascular Agents chapter*)

Case Studies and Conclusions

TC is a 35-year-old mortgage broker who presents to clinic today after a long-standing history of migraine headaches that seems to be worsening with stress at work. He reports he was just evaluated by a neurologist to rule out anything "more serious" and was cleared with normal findings after magnetic resonance imaging (MRI) and neurology workup. He was told that he was unable to use a "triptan" because he is on Zoloft 100 mg daily for depression.

1. Why was TC told he could not take a triptan?

   a. Triptans do not work well for patients who are depressed.
   b. Triptans may increase the risk of serotonin syndrome.
   c. Antidepressants block the triptan receptor.
   d. All of these are true.

Answer B is correct. Triptans (e.g., sumatriptan) exert an influence on serotonin that can cumulatively add increased risk of serotonin syndrome while a patient is taking a serotonin reuptake inhibitor (SSRI) such as sertraline (Zoloft). Triptans work just as well for depressed patients and do not block receptors for antidepressant treatment.

TC would like to take ergotamine because his mother takes this medication and has good results with it.

2. Which dosing recommendation would you make for TC for an ergotamine regimen?

a. 2 mg at first sign of migraine, then 2 mg every 30 minutes if needed
b. Maximum 6 mg per day, 10 mg per week
c. Take only "as needed," as ergotamine is not meant for scheduled administration
d. All of these are true.

Answer D is correct. All of these recommendations are correct.

JP is a 65-year-old male who presents to clinic today with a chief complaint of urgency and feelings of always "having to go to the bathroom." He is otherwise medically healthy and is on no other medication except a multiple daily vitamin.

1. If it is determined that this patient has benign prostatic hypertrophy and is prescribed tamsulosin, which advice would you provide to optimize his medication therapy?

a. Take in the morning so his sleep is not disturbed
b. Time the dose so it is taken a half-hour after a meal
c. Open the capsules and mix them in yogurt
d. May cause hypertension, so monitor his blood pressure

Answer B is correct. The patient should time dose so it is taken 30 minutes after the same meal daily. It is best to avoid morning administration, especially given that the hypotensive effects occur within the first 4 to 8 hours of taking the dose. Capsules cannot be opened or chewed.

A few weeks later, JP describes an "amazing" improvement after taking his tamsulosin. He even comments about an episode where he had an erection that lasted for more than 3 hours and said he would not need to ask for a prescription for Viagra.

2. What would you offer as a response?

a. Tamsulosin can often take the place of Viagra and saves money.
b. Tamsulosin can cause a medical emergency called priapism.
c. Tamsulosin can improve depression and increase libido.
d. All of these are true.

Answer B is correct. Although improvement of the patient's urinary symptoms is a good thing, the emergency of prolonged erections is not. Prolonged erections should be reported promptly, as priapism is a medical emergency that may not resolve without emergency intervention and may have significant negative physiologic consequences.

4.5 Skeletal Muscle Relaxants and Miscellaneous Autonomic Agents

Centrally Acting Skeletal Muscle Relaxants

The action of centrally acting skeletal muscle relaxants is associated with an interrupted communication of neurons within the central nervous system and not a direct effect on the muscle tissue. In addition to decreasing muscle tone and promoting relaxation, the CNS effects also include sedation, which in part is thought to be responsible for altered pain perception. Although overall evidence of comparable effectiveness of drugs within this class is lacking, GABA-derivative antispasmotic agents such as baclofen are known to be more effective when used for muscular spasm associated with multiple sclerosis as compared to those that relieve other musculoskeletal conditions.

Centrally Acting Skeletal Muscle Relaxants

Carisoprodol
Chlorzoxazone
Cyclobenzaprine
Metaxalone
Methocarbamol
Tizanidine

Direct-Acting Skeletal Muscle Relaxants

Dantrolene

GABA-Derivative Skeletal Muscle Relaxants

Baclofen

Neuromuscular Blocking Agents

Atracurium
Cisatracurium
Pancuronium
Rocuronium
Succinylcholine
Vecuronium

Miscellaneous Skeletal Muscle Relaxants

Orphenadrine

Miscellaneous Autonomic Agents

Nicotine is the substance found in tobacco smoke and is well known for its addictive properties. It is not known to be carcinogenic, nor is it associated with the smoking-related adverse effects attributed to the polycyclic aromatic hydrocarbons (PAH) and other chemicals found in cigarettes. The therapeutic use of nicotine replacement has been widely accepted as a mainstay in smoking cessation, allowing the individual the opportunity to have a "controlled withdrawal" from nicotine and a more successful attempt to stay smoke free. Nicotine agonists, such as varenicline, have become increasingly more popular as an alternative aid for smoking cessation although there has been some recent focus on the potential neuropsychiatric side effects reported with their use.

Nicotine
Varenicline

Case Studies and Conclusions

LL is a 55-year-old female who is diagnosed with early-stage lung cancer that appears to be responsive to treatment. She would like to begin a smoking cessation regimen to finally "quit" once and for all.

1. Which of the following nicotine-replacement formulations is NOT dosed according to when the first cigarette of the day is smoked?

   a. Gum
   b. Lozenge
   c. Inhaler
   d. Patch

Answer D is correct. Lozenge strength is determined according to when the first cigarette of the day is smoked (if more than 30 minutes after waking up, use 2 mg lozenge; if less than 30 minutes, use 4 mg lozenge). The gum and inhaler are also dosed based on time to first cigarette smoked (starting doses may also include the total number of cigarettes smoked per day). The nicotine patch is dosed based on the total number of cigarettes smoked within 24 hours.

2. LL smokes roughly ½ pack per day. Which strength of gum would you order for her?

   a. 2 mg gum
   b. 4 mg gum
   c. 6 mg gum
   d. No gum

Answer A is correct. If the patient smokes fewer than 25 cigarettes per day, use 2 mg gum. If the patient smokes more than 25 cigarettes per day, use 4 mg gum. Gum is still an appropriate replacement for this patient if she agrees to it.

A 70-year-old family member calls to ask your professional advice about using varenicline (Chantix) for smoking cessation. She has heard a lot of good and bad things about this drug, but wants to hear what you have to say before talking to her physician.

1. What would you advise your family member about the proper way to use varenicline?

   a. Patients must stop smoking for 1 week prior to the quit date so nicotine is cleared from the body.
   b. Therapy is limited to 12 weeks, so patients must be serious about quitting before starting varenicline.
   c. Patients must get a prescription before the quit date and start the drug 1 week before that quit date.
   d. This patient is too old to take varenicline, so she should use nicotine patches.

Answer C is correct. The varenicline regimen must be established at least 1 week prior to the quit date (some patients require a longer baseline prior to the quit date—refer to the PI). Varenicline engages the nicotine receptors so that even if the patient smokes, he or she will not experience the same degree of reward.

Tips from the Field

Here are some suggestions for improving your patient's technique when using most metered dose inhalers (MDI):

1. Instruct the patient on proper inhalation technique according to the product's directions.
2. Prior to first use (and if not used again for a few days or longer), "priming" is often required.
3. The patient should exhale slowly and fully, and then close the lips around the end of the mouthpiece and inhale slowly, breathing deeply through the mouth, while pressing the dose-release button and continuing to breathe in slowly for as long as possible.
4. The patient should hold the breath for 10 seconds or for as long as comfortable.
5. The mouthpiece (and all other parts as recommended by the manufacturer) should be cleaned with a damp cloth or tissue at least once a week (or more frequently).
6. The inhaler contains a certain number of inhalation doses (products vary significantly regarding this number). Some products have dose indicators showing approximately how much medicine is left. Many inhalers have "beyond use dates" that require discarding the remaining product, even if the inhaler is not empty.

Here are some suggestions for improving your patient's success in smoking cessation:

1. Recognize that tobacco use disorder is a chronic disease and thus patients who are nicotine dependent may have remission and relapse. Be patient, encourage, and motivate!

2. Continue to remind your patients of the overall health benefits of quitting, including both short- and long-term gains.
3. Provide resources to your patients, including nicotine-replacement options. There are many "quit" support programs that may even offer free nicotine replacement.
4. During every episode of care, inquire about nicotine use, counsel about the need to quit, evaluate the willingness of the patient to quit, offer support to assist your patient along the entire spectrum of cessation, and arrange for follow-ups that will help identify problems, challenges, and to celebrate successes, no matter how seemingly small.

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Symbols

- Renal impairment: Dose adjustment is recommended.
- Hepatic impairment: Dose adjustment is recommended.
- Black box warning exists for this drug.
- QTc prolongation effects have been reported.
- Beers list criteria (avoid in elderly).
- FDA-approved pediatric doses are available.
- FDA-approved geriatric doses are available.
- See primary body system.

Autonomic Agents

Universal prescribing alerts:

- Known serious hypersensitivity to the specific drug or any other component of the product/formulation selected warrants a contraindication for use.
- Adverse reactions associated with the use of some **autonomic agents** include dizziness, drowsiness, vertigo, or fatigue; these agents may also impair the ability to perform tasks requiring mental alertness. Caution should always be recommended when using any new drug for the first time, when there is a dose change, and for continued use of known offending agents.
- Doses expressed are for usual adult dosage ranges only. "Geriatric doses" are assumed to be the same as adult doses unless otherwise noted with a symbol. Where pediatric dosing is available, a symbol will guide the reader to additional prescribing references. Refer to real-time prescribing references for these age-specific doses.
- Use of autonomic agents in pregnancy is based on weighing clinical risk versus benefit; safety concerns are not represented in this grid. Refer to the package insert (PI) for more information. Clinicians should continue to provide education about the reproductive risks of any medication and offer risk-reduction strategies (which may include contraceptive use) to women of childbearing age and understand that these reproductive risks may also extend to males. Other medications may decrease the effectiveness of oral contraceptives. When necessary, an alternative means of birth control should be explored.
- Brand names are provided for those agents still available on the market. Due to ever-changing product availability, refer to Food and Drug Administration (FDA) resources to confirm the actual brands available. This drug summary is intended for educational purposes only. Prescribing decisions should be based on real-time comprehensive drug databases that are updated on a regular basis.

Autonomic-Parasympathomimetic (Cholinergic) Agents

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Ambenonium **Brand Name** Mytelase	Myasthenia gravis	Dose depends on the response and clinical status of the patient **Usual oral dose:** Initial: 5 mg 3 or 4 times daily; dose may be increased gradually Usual maintenance: 15 to 100 mg daily	• Drug interactions may require dose adjustment or avoidance of certain drug combinations • Ganglionic blocking agents (e.g., mecamylamine, guanadrel, guanethidine) and routine use of atropine sulfate are contraindicated for use with ambenonium • Use with caution in patients with mechanical gastrointestinal (GI) obstruction (or ileus) or urinary tract obstruction (due to muscarinic effects) • Use with caution in patients with asthma, owing to cholinergic stimulation • Use with caution in patients with Parkinson's disease • Very narrow therapeutic index (overdose may occur with little or no warning)

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls

Generic Name
Bethanechol
 	
Brand Name
Urecholine
	Neurogenic bladder
	
	Urinary retention postoperatively or nonobstructive postpartum and treatment of atonic neurogenic bladder
		Usual oral dose for acute postoperative/ postpartum non-obstructive urinary retention:
		Initial: 5 to 10 mg; may be repeated hourly for effective response or cumulative lifetime dose of 50 mg is given
		
		Usual parenteral dose (urinary retention as above):
		SQ: 5 mg 3 to 4 times per day as needed
			• Administer on an empty stomach to minimize nausea/vomiting (1 hour before or 2 hours after a meal)
			• Do not administer IM or IV
			• Flushing and warmth of the skin (particularly about the face), diaphoresis, and bronchospasm are among the numerous side effects reported with use
			• Use precautions and/or avoid use in patients with:
			  • Chronic obstructive pulmonary disease (COPD)
			  • Hypertension
			  • Ileus
			  • Orthostatic hypotension
			  • Syncope (use caution when driving or operating machinery)
			Contraindications:
			• Asthma
			• Bradycardia or hypotension (pronounced), vasomotor instability
			• Coronary artery disease (CAD)
			• Gastrointestinal or genitourinary (GU) tract, bladder obstruction (or recent surgery)
			• Inflammatory bowel disease (including spastic GI disturbances)
			• Hyperthyroidism
			• Parkinsonism
			• Peptic ulcer disease (PUD)
			• Peritonitis
			• Seizure disorder (epilepsy) or seizure

Generic Name Cevimeline **Brand Name** Evoxac	Xerostomia associated with Sjögren's syndrome	**Usual oral dose:** 30 mg 3 times per day	• May administer with food to lessen GI upset • Excessive sweating in elderly patients may lead to dehydration • May cause decreased visual acuity and impaired depth perception; use with caution when driving or operating machinery especially at night, and in patients with miosis • Use with caution in patients with choledocholithiasis (gallstones in the bile duct) or nephrolithiasis (kidney stones); may induce smooth muscle spasms precipitating cholangitis, cholecystitis, or biliary obstruction in susceptible patients • Use with caution and under close medical supervision in patients with controlled COPD, bronchitis, or asthma

			• Use with caution in patients with cardiovascular disease (especially those with angina or history of myocardial infarction [MI]) or in patients with cardiac arrhythmia; cevimeline may alter cardiac conduction and/or heart rate Contraindications: • Uncontrolled asthma • Narrow-angle glaucoma • Iritis
Generic Name Donepezil **Brand Name** Aricept 	Alzheimer's disease Dementia (mild to severe)	**Usual oral dose for mild to moderate dementia:** 5 mg once daily; may increase to 10 mg once daily after 4 to 6 weeks Moderate to severe dementia requires higher doses; refer to PI	• Available in orally disintegrating tablets • May cause anorexia or weight loss • May cause diarrhea, nausea, and vomiting that are transient and often dose related • Rare cases of neuroleptic malignant syndrome (NMS) have been reported; must evaluate patients and may need to discontinue donepezil if symptoms of NMS emerge • Rare cases of rhabdomyolysis have been reported within a few months of initiating the therapy; monitor creatine phosphokinase (CPK) levels and signs and symptoms such as muscle pain, malaise, fever, and dark urine • Use with caution in patients with peptic ulcer disease • Use with caution in patients with underlying cardiac conduction abnormality, respiratory disease, seizure disorder, and urinary tract obstruction
Generic Name Galantamine **Brand Name** Razadyne 	Alzheimer's disease Dementia (mild to moderate)	**Usual oral dose for mild to moderate dementia:** Immediate release (IR including liquid formulations): Initial: 4 mg twice daily with food If this dose is well tolerated after a minimum of 4 weeks, the dose may be increased to 8 mg twice daily A subsequent increase to 12 mg twice daily may be considered after at least 4 weeks of the previous dose, if well tolerated	• If treatment is interrupted for more than 3 days and then reinitiated, reinitiate therapy with the lowest dose (i.e., 4 mg twice daily) and slowly retitrate to the current dose • Patients should be maintained on their highest well-tolerated dose to achieve maximum benefit • Nausea, diarrhea, and vomiting are the most common side effects (greater than 10% incidence), and may be dose related; take with food and fluids to decrease risk (ensure adequate fluid intake during treatment) • Many dose formulations are available; use caution when ordering • Oral solution dosage should be diluted according to the manufacturer's recommendations immediately prior to administration • All patients should be considered at risk for adverse cardiac effects • Use with caution in patients with peptic ulcer disease, pulmonary disease • May induce or exacerbate urinary tract obstruction and/or bladder obstruction • Avoid in patients with severe renal or hepatic impairment

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
		Alternatively: Extended release (ER): Initial: 8 mg once daily in the morning with food After a minimum of 4 weeks, the dose may be increased to the recommended initial maintenance dosage of 16 mg once daily A subsequent increase to 24 mg once daily may be considered after at least 4 weeks of the previous dose, if well tolerated	• Use should be discontinued at the first appearance of a skin rash, unless the rash is clearly not drug related; if signs or symptoms suggest a serious skin reaction, use of this drug should not be resumed and alternative therapy should be considered
Generic Name Neostigmine **Brand Name** Bloxiverz 	Postoperative nonobstructive abdominal distension (adynamic ileus) Myasthenia gravis Postoperative bladder distension and urinary retention Reversal of nondepolarizing muscle relaxants	**Illustrative doses for adynamic ileus:** IM or SQ: 0.5 mg Need for repeat dosage depends on patient's response; refer to PI	• Bradycardia, hypotension, and dysrhythmia may occur with IV use; risk is increased with cardiovascular disease and myasthenia gravis • Overdose results in cholinergic crisis, characterized by extreme muscle paralysis, extreme muscle weakness, and potentially fatal respiratory paralysis • Large doses of neostigmine administered to reverse minimal neuromuscular blocking agent (NMBA) blockade can result in neuromuscular dysfunction • Use with caution in patients with cardiovascular disease, pulmonary disease (may cause bronchospasm), hyperthyroidism, myasthenia gravis, peptic ulcer disease, seizure disorder, and vagotonia • Elderly patients may require dose reductions, but no specific dosing is currently recommended • Oral dosing is still available for reference in some databases, although there are no commercially available oral dose formulations in the United States Contraindications: • Peritonitis • Mechanical obstruction of intestinal or urinary tract • Hypersensitivity reactions have been reported; have atropine and epinephrine ready to treat hypersensitivity reactions; review patient's allergy and past reaction history

Generic Name Physostigmine PD BL	Reversal of toxic anticholinergic effect Treatment of open-angle glaucoma	**Usual parenteral dose:** IM/IV: 0.5 to 2 mg; may repeat every 10 to 30 minutes until response occurs **Ophthalmic solution for open-angle glaucoma:** 0.25% to 0.5% solution: 1 or 2 drops into each eye up to 4 times daily or ointment applied 1 to 3 times daily	• Avoid in patients with closed-angle glaucoma; worsens blockage of aqueous humor outflow and increases intraocular pressure • Discontinue if excessive cholinergic activity occurs • When administering IV, administer no faster than 1 mg per minute to prevent adverse effects associated with too-rapid administration • Avoid in patients with asthma (can cause bronchcoconstriction) and cardiovascular disease • Use with caution in patients with hypotension and bradycardia (increased vagal tone will worsen these conditions) • May cause alter insulin requirements for patients with diabetes • Use with caution (or avoid) in patients peptic ulcer disease and/or seizures Contraindications: • Gastrointestinal/ileus or urinary obstruction
Generic Name Pyridostigmine **Brand** Mestinol Regonol PD	Myasthenia gravis Reversal of neuromuscular blockade Pretreatment for Soman nerve gas exposure	Different dose formulations are available (including solution/syrup) **Illustrative oral dose for myasthenia gravis:** Immediate release (IR): 600 mg given in 5 to 6 divided doses per day Sustained release: 180 to 540 mg once or twice daily (separated by no less than 6 hours) **Illustrative parenteral dose for treatment of myasthenia gravis:** IV/IM: 2mg every 2 to 3 hours; must be administered slowly Dosing for Soman nerve gas exposure requires specific protocol	• Highly individualized dosage ranges • Discontinue if excessive cholinergic activity occurs, such as excessive salivation, urinary or fecal incontinence, or vomiting • Muscle weakness may be a symptom of myasthenic crisis • Failure of patients to show clinical improvement may reflect underdosage or overdosage (which may result in a life-threatening cholinergic crisis) • Use with caution in patients with cardiovascular disease, as this drug may cause bradycardia or arrhythmias • Use with caution in patients with asthma, COPD, glaucoma, peptic ulcer disease, seizures, or renal impairment • Electrolyte imbalances associated with adrenal cortical insufficiency may enhance or inhibit neuromuscular blockade • No specific dosage adjustment is required for renal impairment, but lower initial doses may be required due to prolonged elimination in renal impairment; titrate dose to effect • IV infusions used for reversal of neuromuscular blockade should be administered only by trained clinicians familiar with the use of these agents (dosing specific to reversal protocol) Contraindications: • Gastrointestinal/ileus or urinary obstruction

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Rivastigmine **Brand Name** Exelon BL	Mild to moderate and severe Alzheimer's disease Alzheimer's dementia Mild to moderate Parkinson's disease dementia (PDD)	**Usual oral dose for Alzheimer's disease:** 1.5 mg twice daily; may increase by 3 mg daily up to 6 mg twice daily **Transdermal patch:** Apply 4.6 mg/24 hours once daily If well tolerated, titrate up to 9.5 mg/24 hours Continue as long as therapeutically beneficial If needed, may increase to 13.3 mg / 24 hours (maximum dose) Dose titrations should occur at no less than 2-week intervals for oral regimens and 4 weeks for transdermal regimens Refer to specific dose strategies when converting to transdermal patch If medication is interrupted (i.e., a few days missed), the dose should be evaluated for restarting at the same, lower, or initial dose based on the formulation and the patient's individualized needs	• Available in oral and transdermal formulations; specific dose forms are indicated for varying degrees of severity of illness, so confirm the correct form prior to use • Take with food • Allergic dermatitis have been reported with transdermal (TD) formulations; discontinue TD therapy if intense local reactions occur • Significant nausea, vomiting, diarrhea or weight loss, and decreased appetite have been reported; occur frequently in women during titration phase; monitor weight during therapy • Cigarette smoking will decrease serum concentrations by roughly 25% • Use with caution in patients with cardiovascular disease (cardiac conduction abnormality), as this drug may cause bradycardia or arrhythmias • Use with caution in patients with asthma, COPD, glaucoma, or seizure • Use with caution in patients with peptic ulcer disease • Patients with hepatic and/or renal impairment may require lower doses; adjust the dose based on individual tolerability and therapeutic needs Contraindications: • Patients who may experience hypersensitivity reactions; review patient's allergy and past reaction history

Autonomic-Anticholinergic Agents

Antiparkinsonian Agents

Benztropine	*Refer to the Central Nervous System chapter.*
Biperiden	*Refer to the Central Nervous System chapter.*
Diphenhydramine	*Refer to Antihistamines*
Procyclidine	*Refer to the Central Nervous System chapter.*
Trihexyphenidyl	*Refer to the Central Nervous System chapter.*

Antimuscarinics/Antispasmodics

Universal prescribing alerts:

- Anticholinergic side effects are a class effect and should be considered to varying degree with all agents in this therapeutic category and others that share anticholinergic side effects (e.g., dry eyes, constipation, worsening of benign prostatic hyperplasia [BPH] and glaucoma). These anticholinergic effects are cumulative (exhibit increased intensity) when multiple agents with this same effect are used concomitantly.
- Use with caution in patients with narrow-angle glaucoma, myasthenia gravis, prostatic hyperplasia/GI or GU obstruction (and other conditions negatively affected by anticholinergic potentiating factors).
- Use with caution in hot weather and during exercise, as these agents reduce the body's ability to sweat and to thermoregulate.
- May cause drowsiness and blurred vision; use with caution while performing tasks that require mental alertness.
- Use with caution in patients with narrow-angle glaucoma, myasthenia gravis, or prostatic hyperplasia/bladder neck obstruction.
- Anticholinergic agents may alter heart rate, with the predominant clinical effect being tachycardia. This action may exacerbate undesirable side effects in patients with hyperthyroidism, hypertension, and underlying cardiac conditions.

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Aclidinium (long-acting) **Brand Name** Tudorza Pressair	COPD	**Usual dose:** 400 mcg (1 actuation) twice daily; maximum daily dose (MDD): 800 mcg	• Rare paradoxical bronchospasms may occur • Immediate hypersensitivity reactions have been reported

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Atropine BL	**Common indications for use:** inhibition of salivation and secretion (aspiration prophylaxis) Bradycardia Neuromuscular blockade reversal GI disorders resulting from cholinergic stimulation Induction of mydriasis	Both the usual and maximum dosages of atropine vary depending on the route of administration and indication for use Clinicians must evaluate the individual patient's response **Illustrative parenteral dose for sinus bradycardia:** 0.5 to 1 mg IV push; repeat if needed every 5 minutes up to 2 mg	• Subject to all the universal prescribing alerts for anticholinergic agents • Avoid use in patients with obstructive neuropathy • Avoid in patients with respiratory conditions; may thicken secretions and dryness (however, anticholinergics may also facilitate bronchodilation depending on dose and route; clinical judgment warranted) • Avoid use in conditions resulting in urinary retention or renal failure • Caution in GI disease or obstruction; decreases GI motility and may cause paralytic ileus • Caution in cardiac patients (especially during MI); may potentiate arrhythmias and may alter heart rate
Generic Name Belladonna BL PD	Moderate pain to severe pain associated with ureteral spasm (bladder spasm) not responsive to non-narcotic analgesics	**Illustrative dose:** 1 suppository rectally 1 to 2 times daily; maximum of 4 doses per day Currently available suppositories contain 16.2 mg belladonna extract with 30 mg powdered opium	• Subject to all the universal prescribing alerts for anticholinergic agents • Few dose formulations are still available; found in combination with other ingredients such as opium • Side effects: fatigue, dry mouth, constipation, vomiting, nausea • Report immediately: severe dizziness, fainting, confusion, tachycardia, vision changes, urinary retention, change in amount of urine passed, sensitivity to light • Precautions: CNS depression, adrenal insufficiency, biliary tract impairment, cardiovascular disease, drug abuse, increased intracranial pressure, prostatic hyperplasia, psychosis, thyroid dysfunction Contraindications: • Glaucoma • Severe renal or hepatic disease • Bronchial asthma • Respiratory depression • Convulsive disorders (seizures) • Acute alcoholism or delirium tremens
Generic Name Dicyclomine **Brand Name** Bentyl	Irritable bowel syndrome	**Usual oral dose:** 20 mg 4 times daily for 1 week; may increase to 40 mg 4 times daily for up to 2 weeks	• Subject to all the universal prescribing alerts for anticholinergic agents • Parenteral formulation for IM use only • Avoid long-term use in elderly patients • Effects of sedatives maybe potentiated with concurrent use • Use with caution in patients with hepatic or renal disease

		Alternative: IM: 20 mg every 4 to 6 hours for 1 to 2 days. Maximum 80 mg per day. Convert to oral therapy as soon as clinically appropriate.	• Increase dose up to 40 mg orally 4 times per day during the first week; if the dosage is not effective within 2 weeks of therapy, or if side effects develop that require doses less than 80 mg per day orally, the manufacturer recommends drug discontinuation • There are no studies on the safety of doses greater than 80 mg per day for periods longer than 2 weeks Contraindications: • Obstructive diseases of GI tract • Severe ulcerative colitis • Reflux esophagitis • Unstable cardiovascular status in acute hemorrhage (and shock) • Urinary tract obstruction • Glaucoma • Myasthenia gravis
Generic Name Glycopyrrolate **Brand Name** Cuvposa Glycate Robinul BL PD	**Common indications for use:** Inhibition of salivation and respiratory secretions preoperatively Bradycardia (specific) Chronic sialorrhea (drooling) COPD	Both the usual and maximum dosages depend on the indication and weight of the patient **Illustrative parenteral dose (preoperative):** IM: 4 mcg/kg 30 to 60 minutes before procedure **Usual oral dose for sialorrhea:** 1 mg twice per day **Usual inhaled dose for COPD:** 2 capsules per day (total of 31.2 mcg) via oral inhalation	• Subject to all the universal prescribing alerts for anticholinergic agents • Diarrhea may occur in patients with ileostomy and colostomy; discontinue if this occurs • Use with caution in patients with cardiovascular disease, hepatic impairment, renal impairment, hyperthyroidism, neuropathy, prostatic hyperplasia, or ulcerative colitis • Avoid in patients with dementia and other cognitive decline (use with caution in elderly patients) Contraindications: • GI or GU obstruction • Myasthenia gravis • Paralytic ileus • Intestinal atony in elderly and debilitated patients • Severe ulcerative colitis • Toxic megacolon complicating ulcerative colitis • Unstable cardiovascular status • Narrow-angle glaucoma • Acute hemorrhage (hemorrhagic shock) • Tachycardia • Oral dosage form: concomitant usage of oral potassium chloride

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Hyoscyamine **Brand Name** Anaspaz Ed-Spaz Hyosyne Levbid Levsin NuLev Oscimin Symax BL PD	**Common indications for use:** Preanesthesia (aspiration prophylaxis) GI disorders (reduces secretion, hypermotility, and spasm in GI) Relaxation of GI tract for diagnostic procedures Bradycardia Urinary system disorder	Doses vary based on indication for use **Illustrative dosing to control gastric secretion or spasm:** Regular-release oral formulations, sublingual and orally dissolvable tablets: 0.125 to 0.25 mg every 4 hours or as needed Extended release: 0.375 to 0.75 mg every 12 hours or 0.375 mg every 8 hours. Maximum of 1.5 mg per day Maximum IV dose depends on indication **Illustrative parenteral dosing:** IV/IM/SQ: 0.25 to 0.5 mg (some patients respond to one dose, others require additional doses, refer to PI)	• Subject to all the universal prescribing alerts for anticholinergic agents • Additional dosage forms are available (elixir, concentrated drops) for special populations • Use with caution in patients with cardiovascular disease, hepatic impairment, renal impairment, hyperthyroidism, neuropathy, prostatic hyperplasia, ulcerative colitis • May cause increased heart rate and result in adverse effects for patients with unstable cardiovascular status (e.g., blood loss, hyperthyroidism, congestive heart failure [CHF]) • Prolonged use may cause dental caries, periodontal disease, oral candidiasis, or discomfort due to decreased salivation • Avoid long-term use in elderly patients Contraindications: • GI or GU obstruction • Glaucoma • Myasthenia gravis • Paralytic ileus • Toxic megacolon • Severe ulcerative colitis
Generic Name Ipratropium **Brand Name** Atrovent HFA Atrovent (nasal spray 0.03% or 0.06%) Ipratropium (oral inhalation)	Cold: symptomatic relief of rhinorrhea Allergic rhinitis Seasonal allergic rhinitis COPD	Depends on route of administration and indication for use **Nasal administration:** 2 sprays in each nostril 2 to 3 times (up to 4 times) per day depending on indication for use and product selected (42 mcg and 84 mcg nasal sprays available for dosing)	• Subject to all the universal prescribing alerts for anticholinergic agents • Limited days duration recommended based on formulation and indication for use • Rare paradoxical bronchospasms may occur; immediate hypersensitivity reactions have been reported • Inhalation/nebulizer can be used in conjunction with beta-adrenergic agonists based on the patient's medical condition and updated guideline recommendations • Nebulizer solution may be mixed with albuterol if mixed and used within an hour; refer to PI for detailed compatibility information • Geriatric and pediatric populations can use a spacer if using the MDI is difficult

		Maximum dose for oral inhalation: Usual: 2 sprays (17 mcg/spray) 3 to 4 times per day, not more often than every 4 hours; maximum 12 sprays (204 mcg) per day via metered-dose inhaler (MDI) Nebulization: 500 mcg (1 ampule/vial) nebulized every 6 to 8 hours	
Generic Name Methscopolamine **Brand Name** Pamine	Adjunctive treatment of duodenal or gastric ulcer	**Usual oral dose:** 2.5 mg 30 minutes before meals and 2 to 5 mg at bedtime	• Subject to all the universal prescribing alerts for anticholinergic agents • Use with caution in patients with prostatic hyperplasia, ulcerative colitis, or other conditions negatively affected by anticholinergic potentiating factors • May cause drowsiness and blurred vision; use with caution while performing tasks that require mental alertness • Use with caution in patients with hepatic or renal impairment • May cause increased heart rate and result in adverse effects for patients with unstable cardiovascular status and cardiovascular disease (e.g., blood loss, hyperthyroidism, CHF) Contraindications: • GI or GU obstruction • Glaucoma • Myasthenia gravis • Paralytic ileus • Toxic megacolon • Severe ulcerative colitis • Patients with unstable cardiovascular status (i.e., hemorrhagic shock)
Generic Name Propantheline BL GD	Adjunctive treatment of duodenal or gastric ulcer	**Usual oral dose:** 15 mg 3 times daily before meals or food and 30 mg at bedtime	• Subject to all the universal prescribing alerts for anticholinergic agents • Use with caution in patients with prostatic hyperplasia, ulcerative colitis, or other conditions negatively affected by anticholinergic potentiating factors

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
		Patients with mild symptoms (or older adults) may see benefit with a 7.5 mg dose	• May cause drowsiness and blurred vision; use with caution while performing tasks that require mental alertness • Use with caution in patients with hepatic or renal impairment • May cause increased heart rate and result in adverse effects for patients with unstable cardiovascular status and cardiovascular disease (e.g., blood loss, hyperthyroidism, CHF) Contraindications: • GI or GU obstruction • Glaucoma • Myasthenia gravis • Paralytic ileus • Toxic megacolon • Severe ulcerative colitis • Patients with unstable cardiovascular status (i.e., hemorrhagic shock)
Generic Name Scopolamine **Brand Name** Transderm-Scop BL PD	**Common indications for use:** **Transdermal:** Prevention of nausea and vomiting associated with: Motion sickness and recovery from anesthesia and surgery **IM injection:** Produce amnesia, sedation, tranquilization, and amnestic effects Decrease salivary and respiratory secretions **Ophthalmic:** Induction of mydriasis or cycloplegia and treatment of iritis or uveitis	**Usual transdermal dose for motion sickness:** Apply 1 patch (1.5 mg) behind the ear at least 4 hours before anticipated need (best 12 hours before); removal instructions are specific to the indication. May reapply once every 3 days. Parenteral dose depends on indication **Illustrative parenteral dosing for nausea and vomiting:** IM, IV, SQ: 0.6 to 1 mg; may be repeated 3 to 4 times per day. Maximum dose: 2.4 mg per day	• Subject to all the universal prescribing alerts for anticholinergic agents • Use with caution in patients with hepatic or renal impairment • May cause increased heart rate and result in adverse effects for patients with unstable cardiovascular status and cardiovascular disease (e.g., blood loss, hyperthyroidism, CHF) Contraindications: • GI or GU obstruction • Myasthenia gravis • Paralytic ileus • Toxic megacolon • Severe ulcerative colitis • Patients with unstable cardiovascular status (i.e., hemorrhagic shock) • Narrow-angle glaucoma

Generic Name Tiotropium **Brand Name** Spiriva PD	Asthma COPD	Maximum dose is indication and formulation specific **Usual inhalation dose for COPD:** 5 mcg per day (2 inhalations of **Respimat** 2.5 mcg/actuation) via oral inhalation **Usual inhalation dose of dry-powder Handihaler inhaler:** 18 mcg (2 inhalations from one powder capsule for dose) per day	• Subject to all the universal prescribing alerts for anticholinergic agents • Use with caution in patients with moderate to severe renal impairment and monitor closely; may be more sensitive to the anticholinergic effects • Administer at the same time each day • May use short-acting beta agonists for "rescue" treatment; tiotropium is not indicated for bronchospasm • May take 4 to 8 weeks to see full therapeutic effects • Use with caution in patients with hepatic or renal impairment Inhalation powder (Spiriva Handihaler): • Instruct patients not to swallow the capsules; cases of inadvertent oral administration have been reported to the FDA • Discard capsules that have been opened and not used immediately • Place a single capsule in the device; press the button to puncture the capsule • Must use the appropriate inhalation technique (should hear or feel the capsule vibrate within the inhaler for proper dosing) • The gelatin capsule might break into very small pieces that pass through the inhaler screen and reach the mouth or throat; advise patients that this is normal and not expected to cause harm • Do not use the Handihaler device for more than one person; clean it according to the package instructions Inhalation spray (Spiriva Respimat): • Instruct the patient on the proper inhalation technique according to the product directions • Prior to first use, must prime the unit (do not remove canister once inserted into the inhaler); repriming after days of non-use is required • Color-coded dose indicator shows approximately how much medicine is left • Discard 3 months after insertion of cartridge into inhaler Contraindications: • GI or GU obstruction • Glaucoma • Myasthenia gravis • Paralytic ileus • Toxic megacolon • Severe ulcerative colitis • Patients with unstable cardiovascular status (i.e., hemorrhagic shock)

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Umeclidinium **Brand Name** Incruse Ellipta	COPD	**Usual dose:** Umeclidinium 62.5 mcg (1 inhalation) every 24 hours	• Subject to all the universal prescribing alerts for anticholinergic agents • Available in combination with other agents • Side effects: pharyngitis, rhinorrhea, muscle spasms, painful extremities, constipation, diarrhea, neck pain • Precautions: bronchospasm, cardiovascular disease, diabetes, glaucoma, hypokalemia, prostatic hyperplasia, bladder neck obstruction, seizure disorder, thyrotoxicosis

Autonomic-Sympathomimetic Adrenergic Agents

Alpha-Adrenergic Agonists

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Midodrine 	Symptomatic orthostatic hypotension	**Usual oral dose:** 10 mg 3 times daily every 3 to 4 hours during daytime when the patient is upright	• May cause bradycardia due to vagal reflex; use with caution when administered with inotropes, and discontinue if signs of bradycardia occur • Use is not recommended in patients with initial supine elevated blood pressure • Use with caution in patients with diabetes • Drug interactions may require adjustment of dose or may require avoidance of certain drug combinations • Use with caution in patients with renal or hepatic impairment • Use only when benefits of this drug exceed potential risks and no safer treatment option exists Contraindications: • Cardiac disease • Acute renal failure • Urinary retention • Pheochromocytoma • Thyrotoxicosis • Persistent and excessive supine hypertension Associated with: • Severe and persistent systolic supine hypertension (especially when using doses of 20 mg or greater) • Emphasize importance of not administering within 4 hours of bedtime or after the evening meal to prevent supine hypertension during sleep

Generic Name	Common indications for use:	Doses vary based on formulation, administration route, and indication for use	• IV, oral, and topical dosage forms exist for specific indications for use; refer to PI for additional information • The same cautions exist with the ophthalmic, nasal, and topical rectal products, because they all may be absorbed systemically • Avoid use in patients with cerebrovascular disease (e.g., cerebral arteriosclerosis, aneurysm, intracranial bleeding, history of stroke) as this drug may increase the risk of cerebrovascular hemorrhage, especially with intravenous use • Use with caution in men with symptomatic, benign prostatic hypertrophy, due to the potential for urinary retention • Some formulations are contraindicated in patients with thyrotoxicosis, including hyperthyroidism, and should be given with caution to patients with diabetes mellitus • Avoid use as an adjunct to anesthesia in the fingers, toes, nose, and genitalia because it can cause severe tissue necrosis due to vasoconstriction of small blood vessels • Use with caution in patients with extensive peripheral vascular disease; can cause excessive vasoconstriction and ischemia to vital organs • Use with caution when administering to patients with hepatic and renal disease: larger doses may be needed in patients with hepatic disease; lower doses may be needed in patients with renal failure Contraindications: • Avoid use in patients with cardiac disease including coronary artery disease and arrhythmias (e.g., severe hypertension, atrial fibrillation, atrial flutter, ventricular fibrillation) • Thyrotoxicosis, including hyperthyroidism • Patients with closed-angle glaucoma; contraindicated for this use (ophthalmic solutions of phenylephrine indicated for open-angle glaucoma) Associated with: • Requires experienced clinician who is knowledgeable in the use of this agent
Phenylephrine ■ QT BL	Open-angle glaucoma Pupillary dilation (uveitis) Eye/ear/nose/throat (EENT) congestion Vasoconstriction (hemorrhoids) Critical care interventions: paroxysmal supraventricular tachycardia (PSVT), hypotension during anesthesia	**Illustrative parenteral dosing for prevention of hypotension or shock:** IM/SQ: 2 to 5 mg, repeated no more often than every 10 to 15 minutes. Maximum initial IM or SC dose is 5 mg **Usual oral dose for EENT congestion:** 10 to 20 mg per dose every 4 to 6 hours, up to 60 mg per day	
Clonidine	Refer to *the Cardiovascular Agents chapter.*		
Guanabenz	Refer to *the Cardiovascular Agents chapter.*		
Methyldopa	Refer to *the Cardiovascular Agents chapter.*		

Beta-Adrenergic Agonists			
Nonselective Beta-Adrenergic Agonists			
Drug Name	**FDA-Approved Indication**	**Adult Dosage Range**	**Precautions and Clinical Pearls**
Generic Name Isoproterenol **Brand Name** Isuprel QT	**Common indications for use:** For use in specific conditions associated with atrioventricular (AV) block or for treatment of Adams-Stokes syndrome Bradycardia	Dose depends on indication for therapy and patient response **Illustrative parenteral dosing for treatment of ventricular arrhythmias secondary to AV block:** IM/SQ: 0.2 mg initially; additional doses are based on route of administration, continued indication for use and patients clinical response	• Use with caution in patients with cardiovascular disease, diabetes, shock, or hyperthyroidism • Stimulates insulin production, may complicate diabetes management Contraindications: • Angina • Preexisting tachyarrhythmias (ventricular, atrial [flutter] and fibrillation) • Cardiac glycoside intoxication
Selective Beta$_1$-Adrenergic Agonists			
Drug Name	**FDA-Approved Indication**	**Adult Dosage Range**	**Precautions and Clinical Pearls**
Generic Name Dobutamine QT	Short-term inotropic management of patients with cardiac decompensation (low output states)	**Usual parenteral dose:** IV: 0.5 to 1 mcg/kg per minute as a continuous infusion, then titrated every few minutes (usual range 2 to 20 mcg per kg per minute titrated as needed depending on the severity of the patient's condition and indication for use)	• Arrhythmias have been reported; ensure that the ventricular rate is controlled prior to starting dobutamine and monitor closely; use with caution in patients with underlying cardiac conditions • Increase in blood pressure is common due to increased cardiac output • Tachycardia may be dose dependent • Correct electrolyte abnormalities to prevent arrhythmias • Patients with hypovolemia should receive adequate fluid resuscitation prior to administration of dobutamine • Use with caution in elderly patients; start at lower dosages (no specific recommendation available from FDA) • Use with caution in patients with renal impairment Contraindications: • Idiopathic hypertrophic subaortic stenosis

Generic Name Dopamine ■ QT PD	Adjunct treatment of shock Short-term treatment of severe, refractory heart failure	Dose depends on indication for use; and patient response **Illustrative dosing for heart failure:** 3 to 10 mcg/kg per minute as a continuous IV infusion Discontinuation schedule recommendations are specific to patient's age and clinical status	• May increase the patient's heart rate • Use with caution in patients with cardiovascular disease (especially post MI, angina, etc.) and in patients with pre-existing vascular damage or occlusive conditions • May cause decreased peripheral perfusion, leading to tissue necrosis and gangrene • Correct electrolyte abnormalities to prevent arrhythmias • Higher doses (greater than 20 mcg/kg per minute) may increase the risk of tachyarrhythmias and abrupt discontinuation may result in significant hypotension Contraindications: • Pheochromocytoma • Uncorrected tachyarrhythmias • Ventricular fibrillation Associated with: • Sloughing and necrosis in ischemic areas; infiltrate the area as soon as possible with normal saline containing phentolamine (refer to PI for proper emergency management)

Selective Beta$_2$-Adrenergic Agonists

Universal prescribing alerts:

- Recently a conversion to the propellant hydrofluoroalkane (HFA) has been made to avoid further depletion of the protective ozone layer in the atmosphere for the many products available for oral inhalation.
- Agents are subdivided into short-acting (SABA) and long-acting (LABA) agents. LABAs have been associated with an increased risk of severe asthma exacerbations and asthma-related deaths; thus the black box warning on their labels states that monotherapy is contraindicated when treating asthma.
- Avoid use with beta blockers, as these will negate the effects of the beta agonists.
- Beta agonists may cause EKG changes, blood pressure, heart rate elevation, elevated blood glucose, and CNS stimulation.
- Generally these agents should be avoided in any patient with increased risk of prolonged QTc.

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Albuterol **Brand Name** ProAir Proventil Ventolin VoSpire QT PD	Acute bronchospasm (i.e., asthma exacerbation) Bronchospasm prophylaxis Exercise-induced bronchospasm	Dosing requirements vary based on indication for use **Illustrative dosing:** Inhaled: metered dose inhaler (MDI): 2 inhalations (90 mcg/actuation) every 4 to 6 hours as needed; maximum 12 puffs per day (inhaler)	• Available in combination products • Rare paradoxical bronchospasms may occur • Use with caution in patients with cardiovascular disease and diabetes • Use with caution in patients with glaucoma hyperthyroidism, hypokalemia, renal impairment, seizures, or any condition (including concurrent medications that cause the same adverse effect) that increases the risk of prolonged QTc

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
		Dry powder inhalation (DPI) also available Oral immediate release tablets/syrup: 2 to 4 mg every 6 to 8 hours; maximum of 32 mg per day Alternatively: Oral extended release tablets: 4 to 8 mg every 12 hours Nebulized: 2.5 mg 3 to 4 times daily as needed; maximum 4 doses per day (nebulizer solution) for oral inhalation	• Usage of a spacer might benefit elderly patients and others that may experience difficulty using MDI • Regular, scheduled daily usage for long-term control of asthma is not recommended • For exercise-induced bronchospasm, use inhalations 5 minutes prior to exercise • Instruct patients on proper inhalation technique according to the product directions
Generic Name Arformoterol **Brand Name** Brovana ■ QT	COPD	**Usual dose:** Oral inhalation via nebulization: 15 mcg twice daily (MDD: 30 mcg)	• Use for maintenance therapy, not for acute bronchospasm; this drug is a LABA • Rare paradoxical bronchospasms may occur • Use with caution in patients with cardiovascular disease and diabetes • Drug interactions may require dose adjustments or avoidance of certain drug combinations • Use with caution in patients with glaucoma, hyperthyroidism, hypokalemia, renal impairment, or seizures • Tolerance may develop Contraindications: • Monotherapy of LABA is contraindicated Associated with: • LABAs have been associated with an increased risk of severe asthma exacerbations and asthma-related death

Generic Name Formoterol **Brand Name** Foradil Aerolizer powder for inhalation Perforomist nebulizer solution ■ QT PD	COPD Asthma: for maintenance treatment of asthma in **patients receiving optimal treatment** with anti-inflammatory asthma agents and who still require an inhaled beta-adrenergic bronchodilator on a regular schedule	**Usual dose for asthma in patients already on an optimal treatment:** Oral inhalation dosage dry powder inhalation Foradil Aerolizer: 12 mcg every 12 hours (MDD: 24 mcg) Maximum dose via nebulizer is 40 mcg per day	• Many formulations available; use caution when prescribing or administering • Rare paradoxical bronchospasms may occur • Highly selective LABA, not a treatment for acute episodes • Use with caution in patients with cardiovascular disease and diabetes • Use with caution in patients with glaucoma, hyperthyroidism, hypokalemia, renal impairment, seizures, or pheochromocytoma • If used for exercise-induced bronchospasm (EIB), inhale 12 mcg (contents of 1 capsule) via Aerolizer at least 15 minutes before exercise; do not repeat dose sooner than 12 hours • Patients already on this drug for scheduled maintenance should not take additional doses for EIB Contraindications: • Monotherapy of LABA is contraindicated Associated with: • LABAs have been associated with an increased risk of severe asthma exacerbations and asthma-related death
Generic Name Indacaterol **Brand Name** Arcapta Neohaler ■ QT	COPD	**Usual dose:** Inhalation: contents of 1 capsule (75 mcg) inhaled once daily	• Available in combination products • Rare paradoxical, life-threatening bronchospasms • Use with caution in patients with cardiovascular disease, diabetes, hyperthyroidism, hyperkalemia, or seizure disorders • Do not use for acute COPD episodes • Do not use with other LABAs; significant numbers of cardiovascular deaths have been reported with excessive sympathomimetic use Contraindications: • Monotherapy of LABA is contraindicated Associated with: • LABAs have been associated with an increased risk of severe asthma exacerbations and asthma-related death • The safety and efficacy have not been established in patients with asthma
Generic Name Metaproterenol QT	Bronchoconstriction in asthma and COPD	**Usual oral dose tablets/ syrup:** 20 mg 3 to 4 times per day MDD: 80 mg Oral inhalation maximum depends on the formulation used	• Many dose formulations available; use care when prescribing and administering • Not recommended in management of asthma because it causes excessive cardiac stimulation • Use with caution in patients with diabetes • Use with caution in patients with glaucoma, hyperthyroidism, hypokalemia, renal impairment, or seizures • Use with caution perioperatively due to its $beta_1$ effects

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Olodaterol **Brand Name** Striverdi Respimat ■ QT	Chronic obstructive pulmonary disease (COPD)	**Usual dose:** 5 mcg per day via oral inhalation (i.e., 2 inhalations per day of Striverdi Respimat)	• May cause pharyngitis • Combination products are available • Do not use as monotherapy for treatment of asthma or for acute bronchospasm • Precautions: cardiovascular disease, diabetes, hyperthyroidism, hypokalemia, seizure disorders, or predisposing risks for QTc prolongation Associated with: • LABAs have been associated with an increased risk of severe asthma exacerbations and asthma-related death • The safety and efficacy in the treatment of asthma have not been established
Generic Name Salmeterol **Brand Name** Serevent Diskus PD QT	Asthma/bronchospasm COPD Exercise-induced bronchospasm	**Usual dose:** 50 mcg (1 inhalation) twice a day	• Do not use for acute bronchospasm • Combination products are available • May cause rhinitis, pharyngitis, cough, rhinorrhea • Precautions: bronchospasm, upper airway symptoms, cardiovascular disease, diabetes, hepatic impairment, hyperthyroidism, hypokalemia, seizures, and patients with predisposing risks for QTc prolongation Associated with: • LABAs have been associated with an increased risk of severe asthma exacerbations and asthma-related death • Should be used in patients with asthma only as adjuvant therapy in patients who are currently receiving but are not adequately controlled on a long-term asthma control medication (i.e., an inhaled corticosteroid)
Generic Name Terbutaline ▲ ■ QT PD	Acute bronchospasm or bronchospasm Prophylaxis in patients with asthma or COPD	**Usual oral dose:** 5 mg per dose every 6 hours up to 3 times daily If side effects occur, reduce dose to 2.5 mg per dose MDD: 15 mg **Illustrative parenteral dosing:** SQ: 0.25 mg per dose, repeat every 15 to 30 minutes; maximum of 0.5 mg per 4 hours	• Rare paradoxical, life-threatening bronchospasms • Use with caution in patients with cardiovascular disease, diabetes, hyperthyroidism, hyperkalemia, or seizure disorders • Avoid in patients predisposed to QTc prolongation

Generic Name Vilanterol **Brand Name** Breo Ellipta (combined with fluticasone) Anoro Ellipta (combined with umeclidinium) ■ QT	COPD	**Usual dose:** One oral inhalation of Anoro Ellipta 62.5/25 (62.5 mcg of umeclidinium and 25 mcg of vilanterol per inhalation) once daily	• Available only as combination with either fluticasone or umeclidinium • May cause pharyngitis, rhinorrhea, muscle spasms, painful extremities, constipation, diarrhea, neck pain • Precautions: bronchospasm, cardiovascular disease, diabetes, glaucoma, hypokalemia, prostatic hyperplasia, bladder neck obstruction, seizure disorder, thyrotoxicosis, high-risk QTc-prolonging agents • Not indicated for relief of acute bronchospasm or asthma; do not use other LABAs concurrently Contraindications: • Use as primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required Associated with: • Increased risk of asthma-related death

Alpha- and Beta-Adrenergic Agonists			
Drug Name	**FDA-Approved Indication**	**Adult Dosage Range**	**Precautions and Clinical Pearls**
Generic Name Droxidopa **Brand Name** Northera ■	Neurogenic orthostatic hypotension	**Usual dose:** Initial: 100 mg 3 times daily; titrate in increments of 100 mg 3 times a day every 24 to 48 hours; maximum of 1800 mg per day	• May cause nausea, syncope, urinary tract infection (UTI), falling, headache, dizziness, and hypertension • Report immediately: severe headache, severe dizziness, fainting, vision changes, or signs of neuroleptic malignant syndrome • Use with caution in patients with cardiovascular disease and renal impairment • Give the last dose no later than 3 hours prior to bedtime Associated with: • May cause or exacerbate supine hypertension; advise patients to elevate the head of bed when resting or sleeping • Monitor blood pressure in supine position and in recommended head-elevated sleeping position; reduce or discontinue if supine hypertension persists
Generic Name Ephedrine QT	Treatment of reversible acute bronchospasm in patients with asthma or COPD Anesthesia-induced hypertension	Dose varies based on patient's clinical condition, indication for use, administration route, and formulation of product selected	• May cause hypertension • Use with caution in patients with cardiovascular disease, diabetes, prostatic hyperplasia, seizures, thyroid dysfunction, and unstable motor symptoms • Use with caution in elderly patients • Avoid in patients with closed-angle glaucoma

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
		Illustrative parenteral dosing for acute bronchospasm: IM/SQ: 12 to 25 mg; may give 50 mg; maximum of 150 mg per 24 hours	
Generic Name Epinephrine **Brand Name** EpiPen QT PD	**Common indications for use:** Anaphylaxis Hypotension/shock Mydriasis during intraocular surgery Treatment of bronchospasm associated with bronchial asthma	Dose varies based on patient's clinical condition, indication for use administration route, and formulation of product selected **Illustrative parenteral dosing for anaphylaxis:** SQ or IM: 0.3 to 0.5 mg may be repeated if necessary every 5 to 10 minutes	• May cause arrhythmias; use with caution in patients with cardiac disease • Pulmonary edema may occur • May cause decreased urine output due to renal blood vessel constriction • Use with caution in patients with diabetes, hypovolemia, Parkinson's disease, hypertension, or hyperthyroidism • There are specific strengths of injection solution for emergency resuscitation and for anaphylaxis; use care when prescribing and administering • Can induce arrhythmias and angina in patients predisposed (i.e., underlying cardiac or cerebrovascular disease) • Use with caution in elderly patients • Avoid in patients with closed-angle glaucoma • IV administration should be reserved for patients who are profoundly hypotensive or in cardiopulmonary arrest refractory to volume resuscitation and several epinephrine injections • IM route preferred over SQ if administered for anaphylaxis • Caution should be observed to avoid extravasation during intravenous administration, as peripheral ischemia, tissue necrosis, and gangrene in the surrounding area can occur due to vasoconstriction
Generic Name Norepinephrine **Brand Name** Levophed ■ QT	Treatment of acute hypotension, cardiogenic shock, or septic shock	**Illustrative parenteral dosing:** IV infusion: 8 to 12 mcg per minute; titrate to desired response Dosage range and maximum dose vary depending on clinical situation; usual maximum is 30 mcg per minute IV continuous infusion	Contraindications: • Hypotension from hypovolemia, except use as an emergency measure to maintain coronary or cerebral perfusion until volume can be replaced • Mesenteric or peripheral vascular thrombosis, unless it is life-saving procedure • Do not use during anesthesia with cyclopropane or halothane • Extravasation may occur; ensure proper needle or catheter placement prior to and during infusion Associated with: • Risk of extravasation; if it occurs, infiltrate the area with diluted phentolamine with a fine hypodermic needle (see the manufacturer's recommendations for further details)

Generic Name Pseudoephedrine **Brand Name** Sudafed BL PD	Symptomatic relief of nasal congestion	**Usual oral dose:** Immediate release (IR): 60 mg every 4 to 6 hours Extended release (ER): 120 mg every 12 hours or 240 mg every 24 hours MDD: 240 mg	• Combination products available (OTC) • Use with caution in patients with diabetes, prostatic hyperplasia, renal impairment, seizure disorder, or hyperthyroidism • Use with caution in elderly patients • When using for self-medication, if symptoms do not improve within 7 days or are accompanied by fever, notify healthcare provider • Discontinue and notify healthcare provider if dizziness, nervousness, or sleepiness occurs Contraindications: • Bronchitis • Closed-angle glaucoma • Coronary artery disease • Emphysema • Hypertension • Peptic ulcer disease • Urinary retention

Autonomic-Sympatholytic (Adrenergic Blocking) Agents

Alpha-Adrenergic Blocking Agents

Nonselective Alpha-Adrenergic Blocking Agents

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Dihydroergotamine **Brand Name** DHE 45 Migranal ■ PD	Migraine headache with or without aura Treatment of cluster headache	**Usual parenteral dose:** IM/SQ: 1 mg at first sign of headache Can be repeated hourly; MDD: 3 mg; maximum dose per week: 6 pm IV: 1 mg at first sign of headache Can be repeated hourly; MDD: 2mg; maximum dose per week: 6 mg	• Ergoid alkaloids have been associated with fibrotic valve thickening • Vasospasms can occur • Can result in decreased blood flow, ECG changes, and hypertension • Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have been reported following the injection • Ergot alkaloids may result in intense vasoconstriction, leading to peripheral vascular ischemia and possibly gangrene • Avoid use in elderly patients; if used, monitor cardiac and peripheral effects closely • Nasal spray may cause local irritation to the nose and throat Contraindications: • Uncontrolled hypertension • Ischemic heart disease • Angina pectoris • History of MI

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
		Usual intranasal dose: 1 spray (0.5 mg) in each nostril Can be repeated every 15 minutes up to a total of 4 sprays Maximum dose per day: 3 mg or 6 sprays Maximum dose per week: 4 mg or 8 sprays	• Silent ischemia • Coronary artery spasm • Hemiplegic or basilar migraine • Peripheral vascular disease • Sepsis • Severe renal and hepatic dysfunction • Following vascular surgery • Concurrent use of ergot alkaloids Associated with: • Serious and life-threatening peripheral ischemia and vasoconstriction
Generic Name Ergoloid mesylates BL	Treatment of cerebrovascular insufficiency in progressive dementia	**Usual oral dose:** 1 mg 3 times daily, up to 9 mg per day Clinical improvement may require weeks of treatment after initiation	• Ergoid alkaloids have been associated with fibrotic valve thickening • Avoid in patients with hepatic impairment • Rare cases of pleural or retroperitoneal fibrosis have been reported with prolonged daily use • Avoid use in elderly patients • Caution in patients with hypotension or bradycardia • Available in a sublingual formulation Contraindications: • Acute or chronic psychosis, regardless of etiology
Generic Name Ergotamine **Brand Name** Ergomar ■	Migraine	**Usual dose:** Sublingual: 2 mg at first sign of migraine, then 2 mg every 30 minutes if needed; maximum of 6 mg per day, 10 mg per week	• Combination products are available • Use with caution (or avoid) in elderly patients • Do not crush or chew the tablets • Side effects: nausea and vomiting • Report immediately: angina, shortness of breath, bradycardia, tachycardia, arrhythmia, edema, severe dizziness, fainting, severe headache, muscle pain, muscle weakness, change in color of hands or feet from pale to blue or red, burning or numbness of hands or feet, or wounds on fingers or toes • Precautions: cardiac valvular fibrosis, cardiovascular effects, ergotism, pleural or retroperitoneal fibrosis • Discontinuation may result in rebound headaches after prolonged use • Drug interactions may require dose adjustments or avoidance of certain drug combinations

			Contraindications: • Peripheral vascular disease • Hepatic or renal impairment • Coronary artery disease • Hypertension • Sepsis • Dialysis Associated with: • Serious and life-threatening peripheral ischemia and vasoconstriction
Generic Name Phenoxybenzamine **Brand Name** Dibenzyline	Pheochromocytoma (associated hypertension and excessive sweating)	**Usual oral dose:** 10 mg twice daily; increase by 10 mg every other day until optimal blood pressure goal is achieved Usual range: 20 to 40 mg 2 to 3 times day	• Drug interactions may require dose adjustments or avoidance of certain drug combinations • Exaggerated hypotensive or tachycardia may occur • Discontinue if symptoms of severe hypotension or angina occur; avoid use in patients with cardiac conditions (e.g., coronary artery disease [CAD], CHF) • Reduced salivary flow may contribute to the development of dental disease • Use with caution in patients with atherosclerosis, renal impairment, or respiratory tract infections • Use with caution in elderly patients, as they are at higher risk of side effects • Long-term use is not recommended, as there are reports of cancer with such use in humans
Generic Name Phentolamine **Brand Name** Oraverse	**Common indications for use:** Management of norepinephrine extravasation (resulting from alpha-adrenergic effects) Diagnosis of pheochromocytoma (phentolamine blocking test) Hypertensive episodes associated with pheochromocytoma (prevention and management) Reversal of oral soft-tissue anesthesia	Dose varies based on indication for use and formulation of medication selected **Illustrative parenteral dose:** 5 to 10 mg (diluted as per manufacturer in specified amount of normal saline) injected into affected extravasation area within 12 hours	• Side effects: nausea, diarrhea, injection site pain, headache, itching • May stimulate gastric acid secretion • Report immediately: angina, tachycardia, arrhythmia, severe dizziness, syncope, severe headache, paresthesia of hands or feet • Precautions: cardiovascular effects Contraindications: • History of MI • Coronary insufficiency • Angina • Coronary artery disease

Nonselective Alpha$_1$-Adrenergic Blocking Agents	
Doxazosin	Refer to *the Cardiovascular Agents chapter.*
Prazosin	Refer to *the Cardiovascular Agents chapter.*
Terazosin	Refer to *the Cardiovascular Agents chapter.*

Selective Alpha$_1$-Adrenergic Blocking Agents

Universal prescribing alert:

- Alpha adrenergic antagonists have been associated with priapism (persistent painful penile erection unrelated to sexual activity). Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Alfuzosin **Brand Name** Uroxatral QT	Benign prostatic hyperplasia	**Usual oral dose:** 10 mg once daily	• Take immediately following a meal to increase absorption • Do not crush or chew tablets • Side effects: headache, reduced strength or energy • Immediately report: severe dizziness, fainting, angina, priapism • Precautions: discontinue with severe or worsening angina, CNS depression, floppy iris syndrome, orthostatic hypotension, priapism, patients with history of tachyarrhythmia or myocardial ischemia, prostate cancer, QT prolongation, severe renal impairment • Drug interactions may require dose adjustments or avoidance of certain drug combinations • Generally well tolerated in elderly patients, as it is a uroselective alpha blocker Contraindications: • Hepatic impairment (moderate to severe)

Generic Name Silodosin **Brand Name** Rapaflo 	Benign prostatic hyperplasia	**Usual oral dose:** 8 mg once daily	• First-dose orthostatic hypotension may occur 4 to 8 hours after dosing • Administer with food • Capsules may be opened and sprinkled over applesauce and consumed within 5 minutes, followed by 8 ounces of water • Side effects: sexual dysfunction, orthostatic hypotension, headache, insomnia, weakness, nasal congestion, rhinorrhea, sinusitis • Report immediately: hepatic impairment, severe dizziness, syncope, angina, priapism • Precautions: floppy iris syndrome, orthostatic hypotension, concurrent use of phosphodiesterase type 5 (PDE-5) inhibitors, concurrent antihypertensive agents, mild to moderate hepatic impairment, prostate cancer, moderate renal impairment • Use with caution in elderly patients, as there is an increased risk of orthostatic hypotension • Discontinuation should be done with a gradual taper Contraindications: • Renal impairment (creatinine clearance [CrCl] less than 30 mL per minute) • Hepatic impairment (severe) • Drug interactions may require dose adjustment or avoidance of certain drug combinations
Generic Name Tamsulosin **Brand Name** Flomax	Benign prostatic hyperplasia	**Usual oral dose:** 0.4 mg once daily 30 minutes after same meal; may be increased to 0.8 mg once daily after 2 to 4 weeks; restart with 0.4 mg daily if interrupted for several days	• Significant first-dose orthostatic hypotension may occur; use caution • Administer 30 minutes after the same meal each day • Do not crush, chew, or open capsules • Drug interactions may require dose adjustments or avoidance of certain drug combinations • Side effects: headache, dizziness, sexual dysfunction, back pain, diarrhea, rhinitis, rhinorrhea, asthenia, infection, drowsiness, insomnia, weakness • Immediately report: severe dizziness, syncope, blurred vision, angina, tachycardia, chills, pharyngitis, dyspnea, priapism • Precautions: angina, floppy iris syndrome, orthostatic hypotension, syncope, concurrent priapism, prostate cancer • Use with caution in elderly patients, as there is an increased risk of orthostatic hypotension
Carvedilol 	Refer to *the Cardiovascular Agents chapter.*		
Labetolol 	Refer to *the Cardiovascular Agents chapter.*		

Beta-Adrenergic Blocking Agents	
Nonselective Beta-Adrenergic Blocking Agents	
Carvedilol 	Refer to *the Cardiovascular Agents chapter.*
Labetolol 	Refer to *the Cardiovascular Agents chapter.*
Nadolol 	Refer to *the Cardiovascular Agents chapter.*
Nebivolol 	Refer to *the Cardiovascular Agents chapter.*
Pindolol 	Refer to *the Cardiovascular Agents chapter.*
Propranolol 	Refer to *the Cardiovascular Agents chapter.*
Sotalol 	Refer to *the Cardiovascular Agents chapter.*
Timolol 	Refer to *the Cardiovascular Agents chapter.*
Selective Beta-Adrenergic Blocking Agents	
Acebutolol 	Refer to *the Cardiovascular Agents chapter.*
Atenolol 	Refer to *the Cardiovascular Agents chapter.*

Betaxolol 	Refer to *the Cardiovascular Agents chapter.*
Bisoprolol 	Refer to *the Cardiovascular Agents chapter.*
Esmolol 	Refer to *the Cardiovascular Agents chapter.*
Metoprolol 	Refer to *the Cardiovascular Agents chapter.*

Skeletal Muscle Relaxants and Miscellaneous Autonomic Agents

Centrally Acting Skeletal Muscle Relaxants

Universal prescribing alerts:

- These drugs cause CNS depression, so patients must be cautioned about performing activities that require mental alertness.

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Carisoprodol **Brand Name** Soma 	Acute musculoskeletal pain	**Usual oral:** 250 to 350 mg 3 times daily and at bedtime	• Use with caution in patients with history of seizures • Use with caution in patients with history of drug abuse; carisoprodol is a DEA-controlled substance • Use with caution in patients with hepatic and renal impairment • Exaggerated effects in may be seen in "poor metabolizers" (Asian patients may be at higher risk) • Increases the effects of sedatives and alcohol • Muscle relaxants are poorly tolerated in elderly patients; avoid their use in the elderly • Recommended for short-term use (2 to 3 weeks) • Abrupt discontinuation may lead to withdrawal symptoms Contraindications: • History of acute intermittent porphyria

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Chlorzoxazone **Brand Name** Lorzone Parafon Forte DSC BL	Muscle pain associated with acute muscle conditions (spasms)	**Usual oral dose:** 250 to 500 mg 3 to 4 times daily; may increase up to 750 mg 3 to 4 times	• Rare episodes of hepatotoxicity have been reported (some fatal); discontinue if patient develops signs of fever, rash, anorexia, nausea, vomiting, fatigue, dark urine, elevated liver enzymes, or jaundice • Use extreme caution or avoid use in patients with renal or hepatic impairment • Muscle relaxants are poorly tolerated by elderly patients due to their potent anticholinergic effects
Generic Name Cyclobenzaprine **Brand Name** Flexeril Amrix Fexmid QT BL GD	Muscle spasms	**Usual oral dose:** Immediate release (IR): 5 mg 3 times daily; may increase to 10 mg if needed Extended release (ER): 15 mg once daily; some patients may require up to 30 mg once daily	• Use with caution in patients with angle-closure glaucoma, increased ocular pressure, or urinary frequency/urgency • Cyclobenzaprine shares the toxic potential of tricyclic antidepressants (TCAs) • Recommended for short-term use (2 to 3 weeks) • Muscle relaxants are poorly tolerated by elderly patients due to their potent anticholinergic effects; also, since there is risk of fatal hepatic toxicity, avoid their use in the elderly • Avoid use in patients with hepatic impairment • Increases sun sensitivity; use appropriate precautions Contraindications: • Hyperthyroidism • Congestive heart failure • Heart block or conduction disturbances • Acute recovery phase of MI
Generic Name Metaxalone **Brand Name** Skelaxin BL	Relief of acute and painful musculoskeletal conditions	**Usual oral dose:** 800 mg 3 to 4 times per day	• False positive Benedict's test results (urine glucose test) has been reported • Not recommended for geriatric use due to anticholinergic effects Contraindications: • Significant impaired hepatic or renal function • Drug-induced hemolytic anemia or other anemias
Generic Name Methocarbamol **Brand Name** Robaxin PD BL	Common indication for use: Muscle spasms associated with acute painful musculoskeletal conditions	**Usual oral dose:** 1.5 g 4 times per day, then decrease 4 to 4.5 g per day in 3 to 6 divided doses **Usual parenteral dose:** IV/IM 1 g every 8 hours for 3 days	• Anticholinergic effects • Avoid in patients with seizure • Extravasation during intravenous administration may result in thrombophlebitis, sloughing, and pain at the injection site; use extra care • Use with caution in patients with hepatic impairment Contraindications: • Renal impairment

Generic Name Tizanidine **Brand Name** Zanaflex 	Muscle spasticity	**Usual oral dose:** Initiate at 2 mg up to 3 times daily (6- to 8-hour intervals); may increase in 2- to 4-mg increments per dose every 1 to 4 days (MDD: 36 mg)	• When discontinuing the drug, gradually taper doses by 2 to 4 mg daily • Avoid use in patients with hepatic impairment • May cause dizziness, xerostomia, fatigue, asthenia, hypotension, sedation, weakness, bradycardia, constipation, nausea, UTI, blurred vision, pharyngitis, rhinitis, and flulike symptoms • Report immediately: signs of hepatic impairment, signs of infection, severe dizziness, behavioral changes, bradycardia, difficulty moving, back pain • Drug interactions may require dose adjustments or avoidance of certain drug combinations • Precautions: hepatic effects, hypotension, syncope, sedation, CNS depression, hallucinations, QTc prolongation • Monitor liver function at baseline and 1 month after maximum dose achieved; monitor blood pressure and renal function

Direct-Acting Skeletal Muscle Relaxants

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Dantrolene **Brand Name** Dantrium Revonto Ryanodex 	Spasticity Malignant hyperthermia	Dose varies with indication for use, formulation selected, and patient's clinical response **Illustrative oral dose:** 25 mg once daily for 7 days; increase to 25 mg 3 times per day for 7 days, then 50 mg 3 times per day for 7 days, then 100 mg 3 times per day (MDD: 400 mg) **Illustrative parenteral dose for malignant hyperthermia:** 2.5 mg/kg continuously until symptoms subside or cumulative dose of 10 mg/kg is reached	• IV administration is formulation specific: refer to PI for guidance • May cause fatigue, flushing, nausea, vomiting, change in voice, drowsiness, headache, rash or itching, kidney stones, abdominal pain, or change in urination • Immediately report: signs of liver problems, signs of infection, loss of strength or energy, shortness of breath, excessive weight gain, swelling of arms or legs, angina, tachycardia, blood in urine, black tarry stools, vomiting blood, change in thoughts, depression, severe abdominal pain, urinary retention, seizures, severe headache, bruising, bleeding, vision changes, severe dizziness, fainting, severe diarrhea, dysphagia, choking, change in speech, injection-site pain • Drug interactions may require dose adjustments or avoidance of certain drug combinations • Precautions: CNS depression, hepatotoxicity, muscle weakness, photosensitivity, cardiovascular disease, hepatic disease, respiratory disease • Avoid extravasation of injectable dantrolene; the pH is high, and tissue necrosis is possible Associated with: • Oral formulation has potential for hepatotoxicity

GABA-Derivative Skeletal Muscle Relaxants			
Drug Name	**FDA-Approved Indication**	**Adult Dosage Range**	**Precautions and Clinical Pearls**
Generic Name Baclofen **Brand Name** Gablofen Lioresal GD	Common indication for use: Spasticity	Dose varies with indication for use, formulation selected, and patient's clinical response **Illustrative oral dose:** 5 mg 3 times daily; may increase by 5 mg per dose every 3 days; do not exceed 80 mg daily	• Gradual dose reduction over 1 to 2 weeks is recommended • Use with caution in patients with renal impairment, as it is primarily renally eliminated • Drug interactions may require dose adjustments • Precautions: CNS depression, ovarian cysts, urinary retention, gastrointestinal disorders, infections, psychiatric disease, renal impairment, respiratory disease, seizure disorder • May cause: drowsiness, confusions, hypotonia, hyperglycemia, headache, nausea, vomiting, hypotension, peripheral edema, convulsions, insomnia, paresthesia, speech disturbance, altered thinking, itching, constipation, xerostomia, diarrhea, urinary retention, urinary frequency, impotence, back pain, weakness, pneumonia
		Illustrative intrathecal dose: Initiate with 50 mcg for 1 dose with 4- to 8-hour observation	• Additional intrathecal doses may be administered based on the specific protocol; refer to the PI; baseline and ongoing lab values are required • Not indicated for all spastic conditions (i.e., not recommended in patients with trauma-induced cerebral lesions, cerebral palsy, intracranial bleeding, parkinsonism, or a prior stroke or cerebrovascular accident) Associated with: • Abrupt withdrawal of intrathecal baclofen has resulted in severe sequelae, leading to organ failure and death • Not for intravenous administration, intramuscular administration, subcutaneous administration, or epidural administration

Neuromuscular Blocking Agents (NMBA)

Universal prescribing alert:

- Certain conditions may potentiate the pharmacological actions of nondepolarizing neuromuscular blockers and may increase the risk of prolonged neuromuscular block. These states include, but are not limited to, dehydration, electrolyte imbalance (hypokalemia, hypocalcemia, hyponatremia, or hypermagnesemia), and severe acid/base imbalance (respiratory acidosis or metabolic alkalosis). Severe acid/base imbalance may alter a patient's sensitivity to NMBAs: respiratory acidosis may enhance neuromuscular blockade and metabolic alkalosis may counteract it. Dehydration and hypothermia can also increase a patient's sensitivity to neuromuscular blocking agents.
- Neuromuscular blocking agents can cause respiratory paralysis as a result of respiratory depression and therefore should be used with caution in patients with pulmonary disease such as chronic obstructive pulmonary disease (COPD).
- Patients with conditions that impair neuromuscular function can experience prolonged or exaggerated neuromuscular block with nondepolarizing agents. These conditions include myasthenia gravis, among others; refer to PI prior to use.
- Patients with history of malignant hyperthermia (MH) should be treated with neuromuscular blocking agents with great caution; malignant hyperthermia can develop in patients receiving general anesthesia.
- Neuromuscular blocking agents stimulate histamine release. The degree of release is agent specific, but all should be used with caution in any condition such as asthma in which a significant release of histamine may be contraindicated.
- Obese patients require special care; refer to PI for each product for details.

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Atracurium ■ PD	Neuromuscular blockade: adjunct to general anesthesia Facilitate endotracheal intubation Provide skeletal muscle relaxation during surgery or ventilation	Dose varies with indication for use, formulation selected, and patient's clinical response **Illustrative parenteral dose:** IV: 0.4 to 0.5 mg/kg, then 0.08 to 0.1 mg/kg administered 20 to 45 minutes after initial dose; repeat dose at 15- to 25-minute intervals if needed	• Rare anaphylaxis reactions have been reported with use • May cause bradycardia; may not have a significant effect on heart rate • Resistance may occur in burn and immobilized patients • Conditions that may antagonize neuromuscular blockade include respiratory alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, denervation, and muscle trauma • Electrolyte abnormalities such as severe hypocalcemia, severe hypokalemia, neuromuscular disease, metabolic acidosis, and myasthenia gravis may potentiate neuromuscular blockade • Drug interactions may require adjustments in dose or avoidance of certain drug combinations • Maintenance of an adequate airway and respiratory support are critical • Initial dose should be reduced in patients with significant cardiovascular disease or history of elevated histamine release Associated with: • Respiratory depression and insufficiency; requires experienced clinician who is knowledgeable in the use of this agent and specialized care setting
Generic Name Cisatracurium **Brand Name** Nimbex PD	Neuromuscular blockade: adjunct to general anesthesia Facilitate endotracheal intubation Provide skeletal muscle relaxation during surgery or ventilation	Dose varies with indication for use and patient's clinical response **Illustrative initial parenteral dose:** IV: 0.15 to 0.2 mg/kg, then repeat doses as per recommendations in PI (individualize dose)	• Rare anaphylaxis reactions have been reported with use • Drug interactions may require dose adjustments or avoidance of certain drug combinations • May cause severe bradycardia (though rare) • Resistance may occur in burn and immobilized patients • Conditions that may antagonize neuromuscular blockade include respiratory alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, denervation, and muscle trauma • Electrolyte abnormalities such as severe hypocalcemia, severe hypokalemia, neuromuscular disease, metabolic acidosis, and myasthenia gravis may potentiate neuromuscular blockade • Maintenance of an adequate airway and respiratory support are critical • Initial dose may be reduced in patients with significant cardiac disease
Generic Name Pancuronium Pancuronium bromide ■	Facilitate endotracheal intubation Provide skeletal muscle relaxation during surgery or ventilation	Dose varies with indication for use and patient's clinical response	• Rare anaphylaxis reactions have been reported; verify allergy and past reaction history • May produce tachycardia secondary to vagolytic activity and sympathetic stimulation • Resistance may occur in burn and immobilized patients

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
	Mechanical ventilation of ICU patients	**Illustrative parenteral dose:** IV: 40 to 100 mcg/kg initially followed by incremental doses of 10 mcg/kg at 25 to 60 minute intervals as needed to maintain muscle relaxation during prolonged surgery	• Conditions that may antagonize neuromuscular blockade include respiratory alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, and denervation, muscle trauma • Electrolyte abnormalities such as severe hypocalcemia, severe hypokalemia, neuromuscular disease, metabolic acidosis, and myasthenia gravis may potentiate neuromuscular blockade • Maintenance of an adequate airway and respiratory support are critical • Classified as long-acting NMBA; its muscular blockade will be prolonged in patients with renal dysfunction • Some protocols recommend use after an initial dose of succinylcholine for intubation • Use with caution in patients with renal and hepatic impairment Associated with: • Respiratory depression and insufficiency; requires experienced clinician who is knowledgeable in the use of this agent and specialized care setting
Generic Name Rocuronium **Brand Name** Zemuron PD	Facilitate endotracheal intubation Provide skeletal muscle relaxation during rapid sequence intubation Mechanical ventilation of ICU patients	Dose varies with indication for use and patient's clinical response **Illustrative parenteral dose for endotracheal intubation:** IV: Initially 0.45 to 0.6 mg/kg Maximum effects typically noted within 3 to 4 minutes and last up to 22 to 30 minutes	• Dosing protocols allow use of ideal body weight (IBW) for obese patients; refer to PI • Some patients (i.e., older adults) may experience prolonged recovery of neuromuscular function after administration • Resistance may occur in burn and immobilized patients • Conditions that may antagonize neuromuscular blockade include respiratory alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, denervation, and muscle trauma • Electrolyte abnormalities such as severe hypocalcemia, severe hypokalemia, neuromuscular disease, metabolic acidosis, and myasthenia gravis may potentiate neuromuscular blockade • Use with caution in patients with pulmonary hypertension, respiratory disease, or valvular heart disease • If extravasation occurs, local irritation may ensue; discontinue administration immediately, and restart in another vein • Drug interactions may require dose adjustment or avoidance of certain drug combinations • Use with caution in patients with hepatic impairment Associated with: • Rare anaphylaxis reactions have been reported; review patient's allergy and past reaction history • Respiratory depression and insufficiency; requires experienced clinician who is knowledgeable in the use of this agent and specialized care setting

Generic Name Succinylcholine **Brand Name** Anectin Quelicin Quelicin 1000 ■ (PD)	Facilitate endotracheal intubation Provide skeletal muscle relaxation during surgery or ventilation Mechanical ventilation of ICU patients	Dose varies with indication for use and patient's clinical response **Illustrative parenteral dose for neuromuscular blockade during short procedures:** IV: Average dose is 0.6 mg/kg (range 0.3 to 1.1 mg/kg) administered over 10 to 30 seconds Alternatively may give: IM: 3 to 4 mg/kg (MDD: 150 mg)	• Dosing protocols allow use of total body weight (TBW) for obese patients; refer to PI • Rare anaphylaxis reactions have been reported • Risk of bradycardia may be increased with second dose; pretreating with atropine may reduce the risk • Use with caution in patients with increased intraocular pressure, intracranial pressure, or gastric pressure • Use with caution in patients with fractures or muscle spasms • Electrolyte abnormalities such as severe hypocalcemia, severe hypokalemia, neuromuscular disease, metabolic acidosis, and myasthenia gravis may potentiate neuromuscular blockade • Use with extreme caution in patients with hyperkalemia Contraindications: • Personal of familial history of malignant hyperthermia • Skeletal muscle myopathies • Acute phase of injury following major burns • Multiple trauma • Extensive denervation of skeletal muscle • Upper motor neuron injury Associated with: • Rare reports of acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death after administration have occurred • Respiratory depression and insufficiency; requires experienced clinician who is knowledgeable in the use of this agent and specialized care setting
Generic Name Vecuronium **Brand Name** Norcuron ■	Facilitate endotracheal intubation Provide skeletal muscle relaxation during surgery or ventilation Mechanical ventilation of ICU patients	Dose varies with indication for use and patient's clinical response **Illustrative parenteral dose:** IV: 0.08 to 0.1 mg/kg	• Drug interactions may require dose adjustment or avoidance of certain drug combinations • Dose must be considered based on the type of anesthesia used (inhalation anesthesia or balanced anesthesia) • Protocol allows for use of IBW for obese patients • Some patients may experience delayed recovery of neuromuscular function after administration • Electrolyte abnormalities such as severe hypocalcemia, severe hypokalemia, neuromuscular disease, metabolic acidosis, and myasthenia gravis may potentiate neuromuscular blockade • Duration of action may be prolonged in patients with renal and hepatic impairment

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
			• Use with caution in patients with cardiac disease or with slower circulation • Resistance may occur in burn and immobilized patients Associated with: • Respiratory depression and insufficiency; requires experienced clinician who is knowledgeable in the use of this agent and specialized care setting • Rare anaphylaxis reactions have been reported; review patients allergy and past reaction history

Miscellaneous Skeletal Muscle Relaxants

Universal prescribing alerts:

- These agents cause CNS depression, so patients must be cautioned about performing activities that require mental alertness.

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Orphenadrine **Brand Name** Norflex BL	Muscle spasms associated with acute painful musculoskeletal conditions	**Usual oral dose:** 100 mg twice daily **Usual parenteral dose:** IM/IV: 60 mg every 12 hours	• Use with caution in patients with cardiovascular disease such as heart failure, cardiac decompensation, coronary insufficiency, tachycardia, or cardiac arrhythmia • Use with caution in patients with history of drug abuse or acute alcoholism, owing to potential for abuse • Use with caution in patients with renal and/or hepatic impairment • Effects of sedatives and ethanol may be potentiated • Muscle relaxants are poorly tolerated by elderly patients due to their potent anticholinergic effects, and their efficacy in elderly patients is questionable • Avoid in patients who have conditions that could be worsened with the use of anticholinergic medications Contraindications: • Glaucoma • GI obstruction • Stenosing peptic ulcer • Prostatic hypertrophy • Bladder neck obstruction • Cardiospasms • Myasthenia gravis

Miscellaneous Autonomic Drugs			
Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Nicotine **Brand Name** Commit Nicoderm CQ Nicolrelief Nicorette Mini Nicorette Refill Nicorette Starter Kit Nicorette Nicotrol Nicotrol NS Thrive	Smoking cessation	Dose varies with indication for use, formulation selected, and patient's clinical response **Nicotine gum:** Every 1 to 2 hours for 6 weeks, then 4 to 8 hours for 3 weeks (MDD: 24 pieces) **Nicotine inhaler:** 6 to 16 cartridges daily; taper frequency of use over 6 to 12 weeks; can use for up to 6 months **Nicotine nasal spray:** 1 dose = 2 sprays (1 spray in each nostril); give 1 to 2 doses per hour; can use for up to 3 to 6 months (MDD: 40 doses) **Nicotine patch:** 14 mg for 6 weeks, then 7 mg for 2 weeks (if patient smokes more than 10 cigarettes per day, start with the 21 mg patch; refer to PI for details) **Nicotine lozenge:** 1 lozenge every 1 to 2 hours for 6 weeks, then 1 lozenge every 2 to 4 hours for 3 weeks, then 1 lozenge every 4 to 8 hours for 3 weeks (MDD: 20 lozenges)	• If patient smokes fewer than 25 cigarettes per day, use 2 mg gum; if patient smokes more than 25 cigarettes per day, use 4 mg gum • Chew gum and "park" until peppery taste is gone • A 21-mg patch available for patients who smoke more than 10 cigarettes per day • Lozenge strength is determined by when the first cigarette of the day is smoked: more than 30 minutes after waking up, use 2 mg lozenge; less than 30 minutes, use 4 mg lozenge • Use with caution in patients with cardiovascular disease, as products increase blood pressure and heart rate • Discontinue if irregular heartbeat or palpitations occur • Avoid use during the immediate post–myocardial infarction period, in patients with serious arrhythmia, and in patients with severe or worsening angina • Use with caution in insulin-dependent diabetic patients • Use with caution in patients with peptic ulcer disease, hepatic impairment, hyperthyroidism, pheochromocytoma, or renal impairment • Inhaler: use with caution in patients with asthma and COPD; bronchospasm has been reported • Nasal spray is not recommended for patients with chronic nasal disorders such as allergy, rhinitis, nasal polyps, or sinusitis • Vivid dreams or sleep disturbances may occur with the transdermal patch • Remove the patch at bedtime and apply a new patch in the morning • In elderly patients, body aches, dizziness, and asthenia are frequently reported • The reversal of increased liver metabolism caused by cigarette smoking will not be mitigated with the use of nicotine replacement; evaluate medication therapy for need to proactively reduce dose

Drug Name	FDA-Approved Indication	Adult Dosage Range	Precautions and Clinical Pearls
Generic Name Varenicline **Brand Name** Chantix Chantix Continuing Month Pack Chantix Starting Starting Month Pack 	Smoking cessation	**Usual dose:** Initial: Days 1 to 3: 0.5 mg daily Days 4 to 7: 0.5 mg twice daily Maintenance (starting day 8): 1 mg twice daily for 11 weeks	• Start varenicline 1 week before QUIT date; patients must consider setting the quit date before starting varenicline • If the patient successfully quits smoking at the end of 12 weeks, may continue therapy for another 12 weeks to help maintain success • If patients could not quit after the treatment but are still motivated to quit, they should be encouraged to make another attempt with varenicline once the contributing factors for failure have been dealt with • May cause CNS depression, which may impair physical and mental abilities; use caution while performing tasks that require mental alertness • Dose-dependent nausea has been reported, which can be transient or persistent • Discontinue treatment if patients experience behavioral or mood changes • Angioedema and serious rashes have been reported; seek immediate medical care • Use with caution in patients with renal impairment; for specific recommendations for patients undergoing dialysis; refer to PI • Seizures can occur in the first month of therapy; weigh the risks against the benefits before initiating therapy • The reversal of increased liver metabolism caused by cigarette smoking will not be mitigated with the use of nicotine replacement; evaluate medication therapy for need to proactively reduce dose Contraindications: • Hypersensitivity or skin reactions to varenicline or any component of the formulation Associated with: • Neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking varenicline • All patients taking varenicline should be observed and monitored for neuropsychiatric events and behavioral changes; FDA review for potential removal of black box warning for serious neuropsychiatric symptoms reported during use is pending