THE DIVERSE PROPERTIES AND USES OF BETA-BLOCKERS

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ABSTRACT

Beta-blockers are a heterogenous class of drugs with diverse properties. They are a pharmacologic agent utilized to treat heart failure and acute myocardial infarction, as evidenced by their long-term beneficial effects on reducing mortality. Used to control heart rate, beta-blockers are also used to treat certain cardiac rhythm disorders, such as atrial fibrillation, and to control angina. In the past, beta-blockers were considered first-line drugs for hypertension but this recommendation has changed. Beta-blockers may pose a risk in patients with asthma and COPD but they may also be effective for patients with mild to moderate asthma or COPD. Pharmacists and pharmacy technicians should have a system in place to signal or alert them of patients with asthma or COPD, as well as the severity of these conditions, when these patients are prescribed beta-blockers.

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Credits: 1.5 hours of continuing education credit

Type of Activity: Continuing education

Media: Internet **Fee Information:** $9

Estimated time to complete activity: 2 hours, including Course Test and course evaluation

Published: March 28, 2022 **Expires:** March 27, 2025

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Educational Objectives: Upon completion of this educational activity, participants should be able to:

1. **Identify** the indications, uses, contraindications and potential side effects of beta-blockers
2. **Compare** the use of beta-blockers, including off-label uses, in multiple clinical settings
3. **Describe** pharmacologic mechanisms of action of beta blockade on the cardiovascular system, including receptor types and pharmacodynamics
4. **Describe** the effects of beta-blockers in diabetes and asthma, and how a pharmacist or pharmacy technician can identity patients at risk

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Introduction

Beta blockers are used mainly in the treatment of heart failure, angina pectoris, and tachyarrhythmias. Other off-label uses of beta-blockers include the management of migraine headaches, performance anxiety, glaucoma, as well as other disorders. The use of beta-blockers has wide acceptance for the management of cardiovascular disorders and provides protective benefits for ischemic heart diseases with regard to morbidity and mortality. Their uses in patients with asthma and COPD is controversial. Beta-blockers may pose a risk in patients with severe COPD but may also be effective for patients with mild to moderate asthma or COPD. Pharmacists and pharmacy technicians should have a system in place to signal or alert them of patients with asthma or COPD, as well as the severity of these conditions, when these patients are prescribed beta-blockers. This course will discuss how prescriptions for beta-blockers should be made, the risks and benefits of beta-blockers and when and how they must be balanced.

The Autonomic Nervous System and Beta-Blockers

The first commercially marketed beta-blocker was propranolol. It was introduced in 1964 under the original trade name Inderal®. Propranolol's effectiveness for the treatment of angina pectoris was quickly recognized. Its inventor, physician and scientist Sir James Black, was said to have revolutionized the management of angina, and this discovery earned him the Nobel Prize in 1988.[1]

The discovery of how this beta-adrenergic receptor antagonist caused changes in the cardiovascular system is complex, but as a class, beta-blockers produce their therapeutic effect on the sympathetic branch of the autonomic nervous system.[2]

Beta-blockers prevent catecholamines from binding to beta receptors and cause an inhibition of sympathetic influence on the target organs.[2] Sympathetic nerve impulses are transmitted by catecholamines. These endogenous substances bind to specific receptors, the alpha and beta-

adrenergic receptors, in the heart, lungs, liver, vascular smooth muscle, and many other areas of the body. The catecholamine-receptor binding is referred to as the "second messenger effect," which, in turn, initiates a specific cellular activity producing a measurable physiological response.[2] For example, when epinephrine binds to the adrenergic receptors in the heart, the physiological response increases the pulse rate, the speed of impulse conduction through the AV nodal system, and the force of the contraction of the myocardium.[2]

Beta-Receptor Classification

There are three types of beta receptors: $ß_1$, $ß_2$, and $ß_3$, classified by their affinity for adrenergic agonists and antagonists. A ligand, or signaling molecule, can be either produced endogenously, or in the case of a beta blocker, synthetically. The type of response secondary to beta receptor stimulation is determined by the ligand, as well as the type and location of the receptor. Sympathetic stimulation effects of the different types and locations are summarized as follows:[2,3]

1. $ß_1$ receptors in the heart: described above as increase in rate, transmission the AV node, and contraction of myocardium.
2. $ß_2$ receptors in smooth muscle, vasculature, liver and other organs and tissues:
    a. pulmonary: bronchodilation
    b. hepatic: gluconeogenesis
    c. systemic vasodilation
3. $ß_3$ receptors in adipose tissue:
    a. metabolic regulation: increased lipolysis and thermogenesis

Pharmacological Effects of Beta-Blockers

Beta-blockers are a heterogeneous group of antihypertensive agents whose primary mechanism of action is to prevent catecholamine binding to beta receptors.[2] The beta-blockers have common and different pharmacological effects, which makes them a strong drug class. What they have in common is their competitive antagonistic action on beta-

adrenoreceptors located in various parts of the body: ß$_1$ (located in the heart and kidney), ß$_2$ (located in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscles, and skeletal muscles), and ß$_3$ (fat cells). The differences in beta-blockers pertain to their receptor selectivity and specificity, intrinsic sympathomimetic activity (ISA), vasodilating properties and metabolism. In the heart, beta-blockers produce a noticeable decrease in pulse rate, but vasoconstriction caused by beta-blockers is a relatively minor effect. The latter effect happens because vascular tone is primarily mediated through the alpha receptors, so in this case, beta receptor blockade is relatively unimportant.[2]

Differentiation of Beta-Blocker Characteristics

Beta Selectivity

There are three generations of beta-blockers.[2-5] The first generation are non-selective, causing a blockade of both ß$_1$ and ß$_2$ adrenoceptors. The second generation are relatively selective for ß$_1$ adrenoceptors and are thus more cardioselective. Dosage of the drug can cause changes in this relative selectivity, particularly when the dosages are high. The third generation of beta-blockers have a selectivity for the vascular alpha adrenoceptors which causes their vasodilation effects.

There can be variability in the selectivity for these drugs. For example, propranolol will cause beta-blockade at the ß$_1$ and ß$_2$ receptors, but atenolol affects only ß$_1$ receptors. This selectively is relative and not total. For example, metoprolol is relatively ß$_1$ selective but bisoprolol is highly ß$_1$ selective, and acebutolol does not act at ß$_2$ receptors, except at high doses.

Alpha and Beta Blockade

There are beta-blockers, *i.e.*, carvedilol and labetalol, that cause beta blockade at beta and alpha receptors.[2,5]

Intrinsic Sympathomimetic Activity

There are drugs that have agonist and antagonist receptor effects, and this is true of the beta-blockers. Some of the beta-blockers inhibit and stimulate the beta-adrenergic receptors, a characteristic known as intrinsic sympathomimetic activity (ISA), and these beta-blockers do not lower resting heart rate as much as other beta-blockers do. Referred to as partial agonists, the amount of beta stimulation is low grade while at rest, but when sympathetic activity is high, it acts as a typical beta blocker.[4] In addition, beta-blockers with ISA may not have a strong effect on cardiac output, and their vasoconstricting effect may be relatively weak. The benefits and risks of ISA contribute to the complexity of prescribing these drugs. Acebutolol, carteolol, labetalol (at $ß_2$ receptors), penbutolol, and pindolol have ISA.[2,5]

Membrane Stabilizing Activity

Certain beta-blockers have membrane stabilizing activity (MSA). Membrane stabilizing activity is the mechanism of action by which Class I antiarrhythmic drugs work. The sodium ion channels in the cardiac membrane that initiate ventricular depolarization and subsequent ventricular contraction are blocked by MSA, decreasing the responsiveness of the myocardium (stabilizing it) to an action potential, and preventing cardiac arrhythmias. However, if an excess amount of a beta-blocker that has MSA is ingested, *i.e.*, in a deliberate overdose, this effect can be a cause of serious ventricular arrhythmias. It is at very high concentrations that MSA activity occurs, otherwise it is not of much clinical significance.[5] Acebutolol, betaxolol, carvedilol, and propranolol have MSA.

Lipid Solubility

A drug that is lipid-soluble can easily move across cell membranes. Lipid solubility in a beta-blocker allows the drug to enter central nervous system (CNS) tissues that may cause side effects like drowsiness and sedation or be a cause of seizures in a beta-blocker overdose. Penbutolol and propranolol

have high lipid solubility, many of the other beta-blockers, *i.e.,* bisoprolol and metoprolol are moderately lipid-soluble.[2,5]

Serotonin Receptor Activity

Some of the beta-blockers, *i.e.*, propranolol can bind to serotonin receptors, and is proposed as a mechanism of action as to why metoprolol and propranolol have been effectively used as prophylactic treatments for migraine headaches.[2,5] In a review by Danesh and Gottschalk (2019) a comparison was made between beta blocker efficacy and that of other migraine prophylactic medication. It was determined that most often, the dosage of beta-blockers prescribed is too low, but when the optimum dose is given, the results show a favorable comparison with the other migraine medications. It was also noted that this more recent study showed a side effect profile that was more favorable than had been reported in earlier studies.[6]

Beta-Blockers: Pharmacological Profile

There are 15 systemic beta-blockers, several ophthalmic preparations, and a few beta-blockers that are both. This section will briefly review the pharmacologic similarities of the beta-blockers. Important information specific to a beta-blocker will be mentioned, and clinicians are encouraged to continuously review current drug information about any beta-blocker they are administering.

Ophthalmic beta-blocker preparations like timolol can have systemic effects and can cause serious adverse effects *i.e.,* bradycardia, cardiac conduction disorders, hallucinations, hypotension, and syncope.[7,8]

Commonly prescribed systemic beta-blockers include acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, and pindolol.[9]

Pharmacological Category

There are further categorizations made as to the action of beta-blockers which can cross over several classifications. One such drug is acebutolol, with the following multiple descriptors; it is a: Class II antiarrhythmic, antihypertensive, beta-blocker with ISA, beta-blocker, $ß_1$ selective. The seven classifications for beta-blockers are:[2,5,10]

- Antianginal
- Antihypertensive
- Beta-blocker, non-selective
- Beta-blocker, selective
- Beta-blocker with ISA
- Class II antiarrhythmic: Acebutolol, esmolol, propranolol, and sotalol.
- Class III antiarrhythmic: Sotalol.

Mechanisms of Action

As discussed, although the primary therapeutic mechanism of action is beta blockade, some of the beta-blockers also have an alpha blocking effect. The primary effects are on cardiac tissue, with relatively little impact on the vasculature. This is due to the small modulatory role of the $ß_2$ adrenoceptors on basal vascular tone. There is a small degree of vasoconstriction due to the mechanism of beta blockade removal of some of the $ß_2$ adrenoceptor vasodilation influence opposing the influence of the more dominant alpha-adrenoceptor vasoconstriction.[3] Aronson and Green (2020) provide an excellent, recent overview of beta-blockers.[10] The overview includes a description of their mechanisms of action and pharmacological properties. This article also provides an in-depth discussion on the innovations and advances in the development of beta blockers. Aronson and Green also list the beta-blockers that are widely prescribed, and their distinctive actions and uses, which would be useful to pharmacists and pharmacy technicians filling prescriptions for beta-blockers.[10]

Beta-blocker Uses

The beta-blockers are primarily used to treat cardiovascular diseases the labeled uses being for angina pectoris, hypertension (alone or with other drugs), management of ventricular arrhythmias, management of hemodynamically stable patients with known or suspected MI to reduce morbidity and mortality, and treatment of mild to moderate heart failure. The benefit of beta-blockers as first-line therapy for hypertension has been reconsidered recently, and now, without compelling evidence, the indications for treatment with beta-blockers is considered controversial.[10,11] Welton, et al. (2017) in their Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, may be consulted for recommendations of the use of beta-blockers in patients with cardiovascular diseases. These guidelines describe when beta-blockers should be considered as first-, second-, or third-line therapies.[12]

There are some labeled uses that are reserved for specific beta-blockers; however, some may also have several other uses as has been described in this course. Some examples of specific labeled use beta-blockers are:

- Esmolol: Rate control in atrial fibrillation atrial flutter, non-compensatory sinus tachycardia, and intra- and postoperative tachycardia. Although not a typical use, a study was performed using esmolol in a patient with an ST-segment elevation myocardial infarction (STEMI). Er, *et al.* (2016) concluded that smolol treatment significantly decreased troponin T, CK, CK-MB and NT-proBNP release as surrogate markers for myocardial injury in patients with STEMI.[13]
- Labetalol: IV formulation for treatment of severe hypertension.[14]
- Propranolol: Essential tremor, hypertension in pheochromocytoma, infantile hemangioma, migraine headache prophylaxis, and obstructive hypertrophic cardiomyopathy, atrial fibrillation, hypertrophic subaortic stenosis.[15]

- Sotalol: Treatment of dangerous ventricular arrhythmias. Maintaining sinus rhythm in patients who have atrial fibrillation or atrial flutter and are currently in sinus rhythm.[16]
- Timolol: Migraine headache prophylaxis; in addition to prophylaxis, ophthalmic timolol maleate solution showed promise for acute pain from migraine headaches in a randomized crossover clinical trial of fifty patients performed by Kurian, *et al.* (2020); topical timolol was more likely to reduce pain scores 20 minutes after instillation compared with placebo.[17]

Contraindications

Beta-blockers may be contraindicated as a drug class, while in other instances, a specific beta-blocker may be contraindicated but not the entire class. Some beta-blockers may come with warnings requiring that they be used cautiously.

Contraindications that are specific to individual beta-blockers

- Esmolol: Concurrent administration of calcium channel blockers
- Nebivolol: Hepatic impairment
- Sotalol: Long QT syndrome, acquired or congenital
- Metoprolol: Peripheral vascular disease
- Carvedilol: Sick sinus syndrome

Absolute Contraindications to Beta-blockers as a Class

- Symptomatic bradycardia
- Cardiogenic shock and hypotension
- Pheochromocytoma
- Decompensated heart failure

Use with Caution

- Asthma/bronchospastic disease
- Heart conduction abnormalities

- Diabetes mellitus

The use of beta-blockers in patients who have asthma, COPD or diabetes mellitus are discussed here in greater detail.

Patients with Asthma or COPD

Beta-blockers are avoided or used with caution in patients with asthma or COPD.[18] These drugs, particularly the non-selective beta-blockers, can prevent $ß_2$ receptor-mediated bronchodilation, and their use in this patient population can precipitate bronchial obstruction, increase airway reactivity, cause exacerbations, and cause resistance to the beta agonist drugs like albuterol that are used to treat asthma and COPD. The mechanism of action of these effects is not known.

Clinicians should avoid the use of non-selective $ß_1$ and $ß_2$ antagonists like propranolol in patients who have severe or decompensated bronchospastic disease.[19,20] Cardioselective beta-blockers and beta-blockers with ISA can be used for patients who have mild to moderate asthma or COPD, and there is evidence that these drugs are safe for this population.[21] However, clinicians tend to avoid the use of beta-blockers completely or use the smallest, effective dose because receptor selectivity of the beta-blockers is not absolute and the use of selective beta-blockers are not risk-free when given to patients who have asthma or bronchospastic disease.[22,23]

On the other hand, pharmacists and pharmacy technicians should be aware that this hesitancy to prescribe beta-blockers to patients with *moderate* COPD and cardiovascular comorbidity, or sub-dosing the drug out of a fear that beta-blockers may cause or exacerbate bronchospastic disease, could be anecdotal.[24,25] These fears may result in patients with cardiovascular disease who could benefit from a specific type of beta-blocker drug not receiving a prescription or receiving a sub-dose prescription.[24,25]

Zvizdic, *et al.* (2019) studied the use of selective beta-blockers in patients with cardiovascular disease and COPD.[24] They evaluated patients within two groups: moderate COPD and severe COPD. They found that regardless of "the pharmacological treatment, there [was] a statistically significant increase in the number of COPD exacerbations, in a 12-month period follow-up, in the GOLD III group (severe) compared to the GOLD II group (moderate)." This led them to conclude that the "use of selective beta-blockers in the treatment of cardiovascular comorbidity in patients with COPD represents far better choice of pharmacological therapeutic approach in treatment of patients within the GOLD II (moderate) stage of COPD."[24]

Bennett, *et al.* (2021) explained how guidelines have changed from a stricter approach that did not allow the use of beta-blockers in asthma patients unless the prescription of cardioselective β1-blockers were done with specialist supervision, and on a "case-by-case basis."[23] Bennett, *et al.*, concur with other medical scientists in acknowledging that the concerns of prescribing cardioselective β1-blockers for asthma patients leads to an underutilization of beta-blockers in this population.[23] Bennett, *et al.* conclude that "fatalities or serious asthma exacerbations due to cardioselective β1-blocker use are likely to be extremely rare. The reluctance to use cardioselective β1-blockers in people with asthma is not supported by this evidence."[23]

In the end what is clear is that beta-blockers may pose a risk in patients with severe COPD but may also be effective for patients with mild to moderate asthma or COPD. Pharmacists and pharmacy technicians should have a system in place to signal or alert them of patients with asthma or COPD, as well as the severity of these conditions, when these patients are prescribed beta-blockers.[18] A pharmacy computer system is one way to identify these patients.[18] Collecting and updating a patient's medical history is also important. In addition, prescriptions for beta-blockers should be made on a case-by-case basis, the risks and benefits must be balanced, and patients prescribed beta-blockers should be closely monitored.[22-25]

Diabetes Mellitus

There are $ß_2$ receptors in the liver and when blood glucose is below a certain level, stimulation of these receptors by catecholamines (the second messenger effect) initiates gluconeogenesis and glycogenolysis, returning blood glucose to a normal level. There are other ways that endogenous epinephrine increases blood glucose but are beyond the scope of this course.

Beta receptor stimulation is essential for the body's response to hypoglycemia and an important aspect of glucose control, so using beta-blockers for diabetic patients has long been an area of concern. The prescribing information about beta-blockers notes that these drugs should be used cautiously if a patient has diabetes, and hypoglycemia caused by beta-blockers is well documented.[19,26,27] Beta-blockade of $ß_2$ receptors can prevent catecholamines from increasing blood glucose in an individual who is hypoglycemic, and it can blunt the signs and symptoms of hypoglycemia like diaphoresis and tachycardia, putting patients at risk for severe hypoglycemia and preventing self-treatment. They can lack the ability to recognize the signs of impending hypoglycemia.[19,26,27]

The risk for hypoglycemia from beta-blockers in diabetic patients has not been fully quantified. Similarly, the subtypes of beta-blockers need to be individually assessed for diabetics. One such study was performed by Dungan, *et al.* (2019), to determine the relationship between type of beta blocker and incidence of hypoglycemia and mortality in hospitalized patients.[28] They concluded that beta blocker use is associated with increased odds of hypoglycemia among hospitalized patients not requiring basal insulin, and odds are greater for selective beta-blockers than for carvedilol. The odds of hypoglycemia-associated mortality are increased with selective beta blocker use or nonusers but not in carvedilol users, warranting further study.[28]

Beta-blockers can be and are used in diabetics and to do so safely, the following points should be kept in mind:[19,26-28]

- Beta-blockers can cause hypoglycemia

- These drugs have been used safely for diabetic patients.
- There should be a case-by-case assessment of the risks and benefits of using beta-blockers for diabetic patients.
- Diabetic patients who are prescribed a beta-blocker should be closely monitored, they should be taught about the signs and symptoms of hypoglycemia, and informed that the signs and symptoms of hypoglycemia may be blunted by beta-blockers.

Possible Side Effects Associated with Beta-Blocker Use

Side effects known to occur with the use of beta-blockers include bradycardia, depression, exacerbation of heart failure, fatigue, hypotension, drowsiness, sexual dysfunction, and gastrointestinal distress are some of the most commonly reported adverse effects. Bronchospasm and changes in blood glucose and potassium can occur with the use of beta-blockers; these effects will be discussed separately.[9] In addition to these adverse events, labetalol may lead to floppy iris syndrome.[29]

The use of beta-blockers may also be associated with other adverse events. These will be discussed in more detail here. They include hyperkalemia, severe mesenteric ischemia, myasthenia gravis, Prinzmetal angina, psoriasis, and peripheral vascular disease. Beta-blockers may aggravate neuropsychiatric disorders and thyroid disease. Patients with impaired kidney function also require special attention.

Hyperkalemia

Stimulation of $ß_2$ receptors by catecholamines causes potassium to move into cells, lowering plasma potassium levels. Non-selective beta-blockers can prevent this effect, and administration of these drugs has the potential to cause hyperkalemia. However, hyperkalemia caused by beta-blockers is a rare event and should happen only in patients who have pre-existing hyperkalemia or specific medical conditions like end-stage renal disease or hyperaldosteronism.[5-6] The prescribing information for esmolol lists hyperkalemia as a warning.

Mesenteric Vascular Disease

The use of propranolol has been associated with severe mesenteric ischemia.[30,31]

Myasthenia Gravis

There are published reports suggesting that beta-blockers can aggravate myasthenia gravis and/or cause a myasthenic syndrome.[32,33]

Prinzmetal Angina

Beta-blockers, particularly non-selective beta-blockers, may worsen and/or precipitate Prinzmetal angina, Prinzmetal Angina, which is also known as coronary artery spasm or vasospastic angina.[34,35]

Psoriasis

Wu, *et al.* (2014) reported that chronic use of beta-blockers may increase the risk of developing psoriasis.[36] This is not the case with other anti-hypertensive drugs in this study.[36,37]

Peripheral vascular disease

Beta-blockers may worsen the symptoms of peripheral artery disease or Raynaud phenomenon. However, there appears to be no adverse effect on mild to moderate claudication symptoms when beta-1 selective blockers are used.[38]

Neuropsychiatric Effects

Beta-blockers can be an effective drug for managing neuropsychiatric disorders; however, special care is required for the selection of a beta-blocker for a specific patient, especially an elderly patient.[39] Neuropsychiatric effects from the use of beta-blockers may include "fatigue, depression, sleep disorders and nightmares, hallucinations, delirium, Parkinson's disease, or the risk of falling."[39] A clinician should review the pharmacological characteristics of the drug class being considered to determine the *type* of beta-blocker to

select for a patient. The clinician must weigh the pros and cons of a specific beta-blocker for a patient, which means considering the potential *side effects* of the drug being contemplated. A patient should also be monitored for dose amounts and side effects *throughout the treatment*.[39] For example, hydrophilic beta-blockers could be appropriate for an elderly patient but much remains to be learned regarding their effects on the CNS so monitoring could help address any side effects from a drug.[39]

Renal Injury or Failure

First generation beta-blockers may reduce renal output.[9] With second generation drugs such as atenolol or metoprolol (often used as a cardioselective agent), metoprolol is preferred in patients with chronic kidney disease or unstable renal function because metoprolol is cleared through the liver and its dose does not need to be adjusted. Atenolol is cleared through kidneys so the drug can "accumulate in patients with renal impairment (CRCL <35 mL/minute per 1.73 m2)."[4]

Beta-blockers have also been reported to change renal hemodynamics, but studies are limited.[40] They can impact glomerular filtration rate (GFR) and renal plasma flow, so for many beta-blockers, doses may have to be decreased when a patient has renal impairment as determined by creatinine clearance level. Use of beta-blockers, however, is not ruled out in certain conditions, despite the presence of renal impairment.[40-42] It is not uncommon for patients with heart failure and a reduced ejection fraction to concurrently have moderate to severe renal impairment. Beta-blockers tend to be underused in this condition as their effectiveness has been unclear even though they might offer life-saving therapy. A study was undertaken by Kotecha, *et al.* (2019), to evaluate the prognosis of patients and the efficiency of beta-blockers in those with renal impairment, referencing the eGFR as the indicator of responsiveness.[41] Their investigation led to the surprising conclusion that in patients with heart failure, left ventricular ejection fraction <50% and sinus rhythm should receive beta-blocker therapy even though they had concurrent moderate or moderately severe renal dysfunction.[41] Ongoing studies were recommended for those with severe renal dysfunction (eGFR <30 ml/min/1.73

m2), since there were insufficient numbers of patients to evaluate participants with such a low eGFR.[41]

Beta-blockers have shown efficacy in treating patients with chronic systolic heart failure and chronic kidney disease.[43] There is insufficient evidence to recommend beta-blockers in patients with chronic kidney disease only.[43]

The research continues into the use of beta-blockers in a setting of renal impairment. Clinicians should check the most current prescribing recommendations for each drug.

Thyroid disease

Beta-blockers can be effectively used for symptom reduction to manage the increased beta-adrenergic tone caused by hyperthyroidism, including autoimmune hyperthyroidism.[44] They are not indicated for hypothyroidism.[44]

Unfortunately, the contradictions and warnings for the beta-blockers can be variable and at times, contradictory. For example, the prescribing information for some beta-blockers lists asthma/bronchospastic disease and hepatic impairment as contraindications to their use, but for others these conditions are listed as warnings; the beta-blocker can be given if the patient has asthma or hepatic impairment if the risk-benefit ratio favors its use and with careful monitoring. Pertaining to use in patients with liver dysfunction, it has been noted that in taking propranolol, some elevations have occurred in serum aminotransferase levels but only in less than 2% of patients. These elevations usually are transient and do not cause symptoms.[45,46]

Several beta-blockers, but not all, list Prinzmetal angina as a warning, especially those with nonselective adrenoceptor blocking effects, due to the possibility of aggravating symptoms of this vasospastic form of angina. Another example is with the prescribing information for sotalol listing acquired or congenital long QT syndrome as a contraindication and as a warning.[47]

These inconsistencies are confusing, and they reflect, in part, lack of knowledge and research regarding the use of beta-blockers for patients who have these medical conditions, and they certainly present a challenge to clinicians who prescribe and administer these drugs. The prudent and safe approach is to do a case-by-case assessment of benefits and risks and thoroughly review a patient's medical history prior to starting therapy with a beta-blocker.

Dose Adjustment

Hepatic Impairment

The prescribing information for some beta-blockers do not mention dose adjustment for patients who have hepatic impairment but this is not the case for every drug. The prescribing information for nebivolol lists hepatic impairment as a contraindication to its use, while other beta-blockers consider this disease state as a warning; use the drug cautiously in these patients. The non-selective beta-blockers have been used for many years to increase portal circulation in patients who have ascites and cirrhosis,[48] but the safety of even this well-established therapy has been questioned.[49]

A study on beta-blockers to prevent decompensation of cirrhosis with portal hypertension was an investigator-initiated, double-blind, randomized, controlled trial by Villanueva, *et al.* (2019). This study reported that long-term treatment with beta-blockers could increase decompensation-free survival in patients with compensated cirrhosis and clinically significant portal hypertension. The primary means by which this was accomplished was by decreasing the overall incidence of ascites.[46] Hepatic elimination of the beta-blockers is a secondary way in which they are cleared from the body. The risks and benefits of beta-blocker administration should be individually assessed for each patient, with current drug information and/or a specialist in consultation before initiating treatment, and with close monitoring.

Renal Impairment

As mentioned above, renal impairment may affect the choice of beta-blocker prescribed, and the dose. The prescribing information should be consulted to determine the best practice approach for a specific drug.

Drug-drug Interactions

Drugs that affect blood pressure, heart rate or the cardiac conduction system should be used cautiously when the patient is taking a beta-blocker.[50] There are many commonly used medications that can interact with beta-blockers. Patients taking certain antidepressants and a beta-blocker can be at risk for adverse events such as bradycardia, hypotension and falls, particularly in antidepressant drugs which are inhibitors of cytochrome P450 2D6 liver enzymes (CYP2D6).[50] This inhibition would potentiate the plasma levels of the beta blocker, increasing the beta blocker effects. Shin, Hills and Finley (2020) studied whether initiating antidepressant medication in a patient who was already taking a beta-blocker would increase the risk of a hemodynamic event. They found an association of risk for serious adverse events when initiating an antidepressant to a patient taking beta-blockers, and this was observed as a greater risk to those receiving antidepressants which inhibited the CYP2D6 enzyme. Increased morbidity was suggested to have been mediated by a metabolic drug interaction.[50] The significance of consulting a reliable source for drug interactions before administering a drug to a patient currently taking a beta blocker cannot be overly stressed.

Pregnancy and Breastfeeding

Most of the beta-blockers are pregnancy category C and several are category B or D.[51-53] Beta-blockers can cross the placenta.[54]

The use of beta-blockers during pregnancy is controversial.[54] Studies regarding beta-blockers as a cause of congenital malformations have presented conflicting information and these drugs have been associated with low birth weight, fetal bradycardia, and bradycardia, hypoglycemia and other

adverse effects in neonates.[51-53] However, hypertension during pregnancy is increasing, and beta-blockers are commonly prescribed to pregnant women.[55]

A study from the National Birth Defects Prevention Study found a 2-fold increase in the risk for congenital heart defects with beta-blocker use early in pregnancy.[53] Bateman, *et al.* (2018) suggest that this drug usage, during the first trimester, was "not associated with a large increase in the risk for overall malformations or cardiac malformations, independent of measured confounders."[55] When a clinician considers prescribing a beta-blocker to a mother early in her pregnancy, Bateman, *et al.*, recommend balancing the risk to the fetus against the consequences of the mother's hypertension going untreated during pregnancy.[55]

The prescribing information typically states that these drugs are not recommended for use during pregnancy, but that the risk to the fetus from uncontrolled maternal hypertension must be considered. Labetalol is considered an appropriate choice for treating chronic hypertension in pregnant women.[51]

Beta-blockers can be excreted in breast milk, they have been detected in the serum of breastfeeding infants, and clinical effects in breastfeeding infants, *i.e.*, bradycardia have been reported. The information on the use and the safety of beta-blockers during breastfeeding is incomplete, and specific recommendations vary from drug to drug. Examples include atenolol, which has "... relatively extensive excretion into breast milk and its extensive renal excretion, other agents may be preferred while nursing a newborn or preterm infant or with high maternal dosages. Infants older than 3 months of age appear to be at negligible risk for adverse effects from atenolol in breastmilk."[56] Another example is "Because of the low levels of *metoprolol* in breastmilk, amounts ingested by the infant are small and would not be expected to cause any adverse effects in breastfed infants. Studies on the use of metoprolol during breastfeeding have found no adverse reactions in breastfed infants. No special precautions are required."[56]

Withdrawal Warning

Prescribing information for beta-blockers contains a US boxed warning, commonly called a black box warning, that states that abrupt discontinuation of a beta-blocker has been reported to exacerbate angina pectoris and cause acute myocardial infarction. This effect is probably due to upregulation of beta receptors during beta-blocker therapy and increased receptor sensitivity to catecholamines. Prescribing information and authoritative sources recommend that discontinuation of beta-blocker therapy should be over a 1-2-week period, especially if the patient has ischemic heart disease.[19,57]

Beta-blockers and Cardiovascular Diseases

Angina Pectoris

Angina pectoris is defined as a transient pain or pressure in the chest that is caused by myocardial ischemia. Myocardial ischemia is a result of an imbalance between myocardial oxygen demand and supply, and for most people angina pectoris is typically caused by atherosclerotic heart disease. Anginal attacks produce a diffuse chest pain or chest pressure, they typically last for 2-5 minutes, and they are relieved by rest and nitroglycerin. Angina pectoris is very common: approximately 10 million Americans suffer from the disease. Among adults ≥40 years old, 4,469,934 US adults are estimated to have physician-diagnosed angina. Of the patients with angina, 2,757,171 (61.7%) were on β-blockers.[18]

Preventing angina attacks and increasing exercise tolerance are the primary goals for treating angina, and lifestyle changes, including smoking cessation, should be a part of treatment recommendations.[21] Beta-blockers were originally developed to treat angina pectoris that was unresponsive to nitrates. This is still a primary use for these drugs, and beta-blockers are the first-choice drug therapy for patients who have chronic, stable angina, particularly exertional angina.[57-59] Beta-blockers decrease myocardial oxygen demand by decreasing heart rate, myocardial contractility, and stress on the left ventricle; and it has been conclusively shown that beta-blockers improve

exercise capacity, reduce the number of angina attacks, reduce exercise-induced ST segment depression and reduce the need for sublingual nitroglycerin.

All beta-blockers have been proven to be effective as a treatment for chronic angina, but $ß_1$ selective agents are preferred because the non-selective beta-blockers do not have any comparative advantages and they have some potential disadvantages. The treatment goals when using beta-blockers for angina pectoris are to: 1) reduce the frequency and severity of anginal attacks, 2) improve exercise tolerance, 3) attain a resting heart rate of 50-60 bpm, 4) decrease blood pressure and heart rate during exercise, and 5) use the lowest effective dose that is effective that does not produce side effects.

Atrial Fibrillation

Beta-blockers are, and have been used, for attaining rate control of atrial fibrillation and for maintaining sinus rhythm in patients who have atrial fibrillation. Atrial fibrillation is the most common arrhythmia. It is characterized by ectopic atrial activity and an irregular, often rapid ventricular response. Atrial fibrillation is a significant cause of morbidity and mortality, increases the risk of developing heart failure and thromboembolism, and is a common cause of stroke.

Rate control is one of the primary goals of treating atrial fibrillation. In most cases it is preferable to rhythm control, and rate control improves quality of life, decreases the potential for developing tachycardia-induced cardiomyopathy, and reduces morbidity.

Beta-blockers are commonly used to attain acute and chronic rate control in patients who have atrial fibrillation and unless the patient has a pre-excitation syndrome, cannot tolerate a beta-blocker, or has a medical condition that makes use of a beta-blocker problematic, they are the first-choice drug for chronic rate control.[60,61] Their effectiveness at attaining rate

control has been conclusively proved and for this purpose they are superior to the calcium channel blockers and digoxin.[60,61]

The beta-blockers also are more effective than the calcium channel blockers and digoxin at controlling heart rate during exercise. Rate control of atrial fibrillation is a labeled use of esmolol, propranolol, and sotalol; for the other beta-blockers it is an unlabeled use, but they are commonly used for this purpose. For acute rate control, an intravenous (IV) beta-blocker is recommended, either esmolol, metoprolol, or propranolol. Esmolol has a rapid onset of action and a short duration of action, 10-20 minutes, the latter being an advantage if the patient does not tolerate beta-blocker therapy.

Esmolol

Start with 0.5 mg/kg bolus over one minute, followed by 50 mcg/kg/min. Assess the patient after 4 minutes, and if the response was inadequate, continue giving bolus doses while increasing the mcg/kg/min infusion dose. Another method of administration is to start a 50 μg/kg/min infusion without bolus doses and increase the infusion rate every 30 minutes by 50 mcg.

Metoprolol

Start with an IV bolus of 2.5- 5.0 mg over two minutes. This dose may be repeated every five minutes up to a total dose of 15 mg.

Propranolol

Give a 1 mg bolus dose over one minute, repeat this dose every two minutes as needed, three doses maximum.

Sotalol

Sotalol is a non-selective beta-blocker and a Class II and Class III antiarrhythmic.[62,63] It has a labeled use for maintaining sinus rhythm in

patients who have atrial fibrillation and are currently in sinus rhythm, and it has been used for this purpose for many years.[63,64] Sotalol is unique among the beta-blockers as it is the only drug of this class that has a proven benefit of preventing atrial fibrillation.[65,66] Sotalol is contraindicated for patients who have acquired or congenital long QT syndrome,[67] uncontrolled asthma, cardiogenic shock, sinus bradycardia, second degree heart block (unless the patient has a cardiac pacemaker), or uncontrolled heart failure.[68] The dose must be carefully titrated and because of the risk of arrhythmias, initiation of therapy with sotalol should be done in a hospital and using continuous hemodynamic and cardiac rhythm monitoring. There is an IV preparation of sotalol, but it is seldom used.[68]

For chronic rate control of atrial fibrillation, atenolol, bisoprolol, carvedilol, labetalol, metoprolol, nadolol, pindolol, and timolol can be used.[69] They all lower heart rate by decreasing sympathetic tone and although there are advantages and disadvantages associated with each drug, there does not appear to be any significant difference in their effectiveness.[69] Rate control therapy has been characterized as either strict or lenient; strict control is a resting heart rate of < 80 beats/min. and < 110 beats/min during moderate exercise, and lenient control is a resting heart rate < 110 beats/min. Each approach has risks and benefits, and the decision as to which one to use should be made on a case-by-case basis.

Mild to Moderate Heart Failure

Heart failure is a very common cardiovascular condition. According to the CDC, approximately 6.2 million adults in the US have heart failure. In 2018, heart failure was mentioned on 379,800 death certificates (13.4%).[70] As the population gets older and the risk factors for the development of heart failure are endemic to Americans, it is a reasonable assumption that millions of people will continue to develop heart failure. The basic pathologic mechanism of the disease is an inability of the left ventricle to fill with and eject blood. There are many causes of heart failure (and various categories of the disease, as well) including (but not limited to coronary artery disease, hypertension, myocardial infarction, and lifestyle factors like diet, cigarette

smoking, and obesity. But the impact of the disease is the same regardless of why heart failure happens; the heart cannot pump enough blood to meet the metabolic demands of the body. In late stage, severe heart failure, any level of physical activity is difficult and tiring and the patient will be dyspneic even while at rest.

Long-term use of beta-blockers, specifically bisoprolol, carvedilol, and sustained release metoprolol, has been proven to be an effective treatment for heart failure,[71-73] and in the 2016 ACCF/AHA guideline for the management of heart failure, the American College of Cardiology and the American Heart Association wrote: "*Use of 1 of the 3 beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF [heart failure with reduced ejection fraction] unless contraindicated, to reduce morbidity and mortality*."[73] Long-term treatment with beta-blockers can lessen the symptoms of HF, improve the patient's clinical status, and enhance the patient's overall sense of well-being. In addition, like ACE inhibitors, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization.[73]

The beta-blockers will also reduce the rate of cardiovascular events, increase ejection fraction and improve left ventricular remodeling. Beta blocker therapy should be started at very low doses and the dose doubled at regular intervals (for example, every two to three weeks) until the target dose is reached or symptoms (worsening HF) become limiting or symptomatic hypotension or excessive bradycardia develops.[73]

The prescribing information for beta-blockers indicates that these drugs are contraindicated for patients who have severe heart failure. The beta-blockers are routinely prescribed for patients who have heart failure and a reduced (<40%) ejection fraction, but they should *not* be used if heart failure is quite advanced (New York Heart Association Class IV heart failure), if the patient has had an exacerbation of heart failure in the previous 4 weeks, or the patient has signs of congestion like ascites and significant peripheral edema.[73]

Hypertension

Hypertension is a leading cause of death and high blood pressure significantly increases the risk for developing atherosclerosis, heart disease, kidney disease, stroke, and retinal damage.[75,76] Blood pressure control is critically important for preventing hypertensive complications. Lifestyle changes like smoking cessation and weight loss can significantly lower blood pressure, but many people who have hypertension require treatment with an antihypertensive.

Treatment of hypertension is a labeled use for beta-blockers, but they are not a first or second-line choice, particularly for patients who are over the age of 60.[75,76] They are effective at lowering blood pressure, but their use in hypertensive patients has been associated with a higher risk for myocardial infarction and stroke than medications like angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers.[75,76] In addition, the beta-blockers are less effective for African American patients and their use increase the risk of "glucose intolerance, the development of new-onset diabetes, fatigue, and sexual dysfunction."[77]

Current guidelines recommend angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), a thiazide diuretic, or a calcium channel blocker, alone or in combination as the primary treatment for hypertension. Beta-blockers can be added to the treatment regimen if these medications and lifestyle modification have not reduced blood pressure to the target level.[75,76]

Myocardial Infarction

Treatment with a beta-blocker is considered standard care for patients who have had an acute ST-segment elevation myocardial infarction (MI).[78.79] Beta-blockers decrease oxygen demand, decrease the risk for ventricular fibrillation, have a positive effect on ventricular remodeling, decrease automaticity, reduce infarct size, and decrease the short-term and long-term risk of mortality.[78,79] The post-MI use of beta-blockers began before

fibrinolytic therapy, percutaneous coronary intervention, anti-platelet aggregation medications, the use of statin drugs, and it is possible that the absolute magnitude of the mortality benefit from beta blocker described below may be smaller due to the beneficial impact of these preventative medications as well as the use of reperfusion therapies.[80,81] This has led some researchers to conclude that the beneficial post-MI effects of beta-blockers, such as mortality reduction, may not be as strong as was previously though.[82] However, authoritative sources still recommend their use in this clinical situation.[82]

There are no universally agreed-upon standards for which beta-blocker to use and for how long.[82] Beta-blockers should not be given to patients who have had an acute ST-segment elevation MI *and* have active bronchospasm, cardiogenic shock, a heart block > first degree unless the patient has a pacemaker, decompensated heart failure, or severe bradycardia.

Ventricular Arrhythmias

The beta-blockers have been successfully used to prevent ventricular arrhythmias in patients who are having an acute coronary syndrome.[74] This is particularly well researched in the arrhythmias of ventricular tachycardia and/or ventricular fibrillation.[74]

Beta-Blocker Overdose

Beta-blocker overdoses are comparatively uncommon. The American Association of Poison Control Centers in their 2016 data reported almost 1700 intentional ingestions of beta-blockers and 13 deaths.[83] However, a beta-blocker overdose can be difficult to treat as these patients may be critically ill, and they may need antidotal therapies.

Toxic Doses of Beta-Blockers

Toxic doses of the beta-blockers cannot be accurately determined. Yet it was noted by Rotella, *et al.* (2020) that beta-adrenoceptor antagonist

poisoning is a common overdose which can lead to significant morbidity and mortality.[84] In this case review, the "overdose" was referred to as "poisoning." The focus of this study was on the treatment of the poisoning, which included multiple forms of therapeutic medications.[84] Published data on the subject is quite limited and consists of case reports (with their obvious limitations) and small case series. Choices must be made however about what is or is not a potentially dangerous dose, and in 2005 a panel of toxicologists published an evidence-based consensus guideline for out-of-hospital management of beta-blocker ingestions. These guidelines apply to accidental therapeutic errors like double-dosing in adults and to exploratory pediatric ingestions, not to deliberate overdose. In summary the panel recommended that "*Ingestion of either an amount that exceeds the usual maximum single therapeutic dose or an amount equal to or greater than the lowest reported toxic dose (whichever is lower) warrants consideration of referral to an emergency department*."[85]

An example of metoprolol toxicity dosages is provided here. The milligram amounts are what is considered a dose that does not require referral to an acute care facility; the patient can be observed at home.

Metoprolol

- Adult: ≤ 450 mg of an immediate release product, or ≤ 400 mg of a sustained release product.
- Pediatric: ≤ 2.5 mg of an immediate release product, or ≤5 mg of a sustained release product.

Beta-Blocker Overdose: Signs, Symptoms, and Treatment

Bradycardia and hypotension are the most common signs of beta-blocker overdose.[86] More serious effects like asystole, heart blocks, and seizures can also occur, although the latter seldom occurs. An overdose of sotalol can cause QT prolongation and torsade de pointes. Bronchospasm can be caused by beta-blocker overdose, but this is uncommon.[25] Hypoglycemia can be caused by an overdose of beta-blockers but this is uncommon.[87]

Beta-blockers that have MSA appear to be particularly dangerous and are more likely to cause arrhythmias. The onset of effects for an immediate release beta-blocker begins soon after the ingestion and certainly within 6 hours after ingestion.[86] The onset of effects from ingestion of a sustained-release beta-blocker may be significantly delayed. Treatment for a beta-blocker overdose is outlined below.

If the patient presents with beta blocker toxicity within 1 hour after ingestion and there are no contraindications to its use, administer a dose of activated charcoal. Establish IV access and start continuous ECG monitoring. Measure serum acetaminophen and salicylate levels and do a 12-lead ECG. Perform a physical examination and get a health history. If the patient becomes bradycardic and/or hypotensive, use IV fluids, atropine, and an IV vasopressor. These therapies - particularly the vasopressors – are unlikely to be effective, especially if the patient is profoundly toxic, so nurses should be prepared to administer calcium, glucagon, high-dose insulin/dextrose, and/or lipid emulsions.

Calcium

Give 1 gram of calcium chloride or calcium gluconate, 10 mL of calcium chloride/30 mL of calcium gluconate. This is given over 10 minutes and the dose can be repeated every 20 minutes for 4 doses. If a continuous infusion is needed, the dose is 0.02–0.04 g/kg/hr. Closely monitor serum calcium and ECGs.

Glucagon

Glucagon bypasses the beta receptors and increases cAMP. Adults should be given a 5-mg bolus over 1 minute; give children an IV bolus of 50 mcg/kg. If the blood pressure and pulse do not increase within 1 -3 after the bolus, give a second dose. If the second dose is successful, begin a continuous IV infusion at 2-5 mg/hour, 70 mcg/kg/hour for children. If the second dose is not successful, more glucagon is unlikely to work.

High-dose Insulin/Dextrose Therapy

There is no standard dosing protocol for high-dose insulin/dextrose therapy, but the basic principles are the same regardless of differing recommendations.

Give a bolus dose of 1 mg/kg of regular insulin. If the serum glucose is < 150-200 mg/dL, give a bolus dose of 50 mL of 50% dextrose. Begin a continuous infusion of regular insulin at 0.5 units/kg/hour; at the same time start an IV infusion of dextrose (usually 10% or higher) to maintain euglycemia. Titrate the insulin infusion as needed (doses of 10 units/kg/hour and higher have been used) and titrate the dextrose infusion and use boluses of dextrose to maintain euglycemia.

High-dose insulin/dextrose will increase blood pressure but have little to no effect on heart rate. Measure serum glucose and potassium frequently, *i.e.*, every 15 minutes, in the first few hours of therapy and continue to monitor these electrolytes and serum magnesium and phosphorus while the patient is being treated. Watch for hypoglycemia for 24 hours after the insulin infusion has stopped as insulin levels can remain elevated for 24 hours.

Lipid Emulsion

Use a 20% solution and give 1.5 mL/kg, infused in over 5 minutes. When the bolus dose has infused, start a continuous infusion of a 0.25 mL/kg of 20% solution and complete this in 30-60 minutes. The second dose can be repeated several times, or the infusion rate can be increased if needed. There is no specific pediatric dosing.

Summary

There are three generations of beta-blockers. The first generation are non-selective, causing a blockade of both $ß_1$ and $ß_2$ adrenoceptors. The second generation are relatively selective for $ß_1$ adrenoceptors and are thus more cardioselective. Dosage of the drug can cause changes in this relative selectivity, particularly when the dosages are high. The third generation of

beta-blockers have a selectivity for the vascular alpha adrenoceptors which causes their vasodilation effects.

The beta-blockers are primarily used to treat cardiovascular diseases the labeled uses being for angina pectoris, hypertension (alone or with other drugs), management of ventricular arrhythmias, management of hemodynamically stable patients with known or suspected MI to reduce morbidity and mortality, and treatment of mild to moderate heart failure.

Contraindications that are specific to individual beta-blockers

- Esmolol: Concurrent administration of calcium channel blockers
- Nebivolol: Hepatic impairment
- Sotalol: Long QT syndrome, acquired or congenital
- Metoprolol: Peripheral vascular disease
- Carvedilol: Sick sinus syndrome

Absolute Contraindications to Beta-blockers as a Class

- Symptomatic bradycardia
- Cardiogenic shock and hypotension
- Pheochromocytoma
- Decompensated heart failure

Use with Caution

- Asthma/bronchospastic disease
- Conduction abnormalities
- Diabetes mellitus

Beta-blockers are avoided or used with caution in patients with asthma or COPD. These drugs, particularly the non-selective beta-blockers, can prevent $ß_2$ receptor-mediated bronchodilation, and their use in this patient population can precipitate bronchial obstruction, increase airway reactivity, cause exacerbations, and cause resistance to the beta agonist drugs like

albuterol that are used to treat asthma and COPD. The mechanism of action of these effects is not known. Clinicians should avoid the use of non-selective $ß_1$ and $ß_2$ antagonists like propranolol in patients who have severe or decompensated bronchospastic disease. On the other hand, cardioselective beta-blockers and beta-blockers with ISA can be used for patients who have mild to moderate asthma or COPD, and there is evidence that these drugs are safe for this population; clinicians, however, tend to avoid the use of beta-blockers completely or use the smallest, effective dose because receptor selectivity of the beta-blockers is not absolute and the use of selective beta-blockers are not risk-free when given to patients who have asthma or bronchospastic disease. In the end what is clear is that beta-blockers may pose a risk in patients with severe COPD but may also be effective for patients with mild to moderate asthma or COPD. Pharmacists and pharmacy technicians should be aware that this hesitancy to prescribe beta-blockers to patients with mild to moderate asthma or COPD and cardiovascular comorbidity, or sub-dosing the drug out of a fear that beta-blockers may cause or exacerbate bronchospastic disease, could be anecdotal. These fears may result in patients with cardiovascular disease who could benefit from a beta-blocker drug not receiving a prescription or receiving a sub-dose prescription.

Pharmacists and pharmacy technicians should have a system in place to signal or alert them of patients with asthma or COPD, as well as the severity of these conditions, when these patients are prescribed beta-blockers. A pharmacy computer system is one way to identify these patients. Collecting and updating a patient's medical history is also important. Pharmacists and pharmacy technicians should be aware that there is a hesitancy to prescribe beta-blockers to patients with *moderate* COPD and cardiovascular comorbidity, or sub-dosing the drug out of a fear that beta-blockers may cause or exacerbate bronchospastic disease, could be anecdotal. These fears may result in patients with cardiovascular disease who could benefit from a beta-blocker drug not receiving a prescription or receiving a sub-dose prescription.

In the end what is clear is that beta-blockers may pose a risk in patients with severe COPD. In addition, prescriptions for beta-blockers should be made on a case-by-case basis, the risks and benefits must be balanced, and patients prescribed beta-blockers should be closely monitored.

The risk for hypoglycemia from beta-blockers in diabetic patients has not been fully quantified. Similarly, the subtypes of beta-blockers need to be individually assessed for diabetics. Beta-blockers can be and are used in diabetics and to do so safely, the following points should be kept in mind:

- Beta-blockers can cause hypoglycemia
- These drugs have been used safely for diabetic patients.
- There should be a case-by-case assessment of the risks and benefits of using beta-blockers for diabetic patients.
- Diabetic patients who are prescribed a beta-blocker should be closely monitored, they should be taught about the signs and symptoms of hypoglycemia, and informed that the signs and symptoms of hypoglycemia may be blunted by beta-blockers.

Side effects known to occur with the use of beta-blockers include bradycardia, depression, exacerbation of heart failure, fatigue, hypotension, drowsiness, sexual dysfunction, and gastrointestinal distress are some of the most commonly reported adverse effects. Bronchospasm and changes in blood glucose and potassium can occur with the use of beta-blockers; these effects will be discussed separately. In addition to these adverse events, labetalol may lead to floppy iris syndrome. Drugs that affect blood pressure, heart rate or the cardiac conduction system should be used cautiously when the patient is taking a beta-blocker.

Beta-blocker overdoses are comparatively uncommon. Toxic doses of the beta-blockers cannot be accurately determined. Bradycardia and hypotension are the most common signs of beta-blocker overdose. More serious effects like asystole, heart blocks, and seizures can also occur, although the latter seldom occurs. An overdose of sotalol can cause QT prolongation and torsade de pointes.

If the patient presents with beta-blocker toxicity within 1 hour after ingestion and there are no contraindications to its use, administer a dose of activated charcoal. Establish IV access and start continuous ECG monitoring. Measure serum acetaminophen and salicylate levels and do a 12-lead ECG. Perform a physical examination and get a health history. If the patient becomes bradycardic and/or hypotensive, use IV fluids, atropine, and an IV vasopressor. These therapies - particularly the vasopressors – are unlikely to be effective, especially if the patient is profoundly toxic, so nurses should be prepared to administer calcium, glucagon, high-dose insulin/dextrose, and/or lipid emulsions.

Course Test

1. **Beta-blockers produce their therapeutic effect on the _____ branch of the autonomic nervous system.**

    a. enteric
    b. sympathetic
    c. parasympathetic
    d. somatic

2. **Beta-blockers' primary mechanism of action is to prevent _____ from binding to beta receptors.**

    a. catecholamines
    b. acetylcholine
    c. amino acids
    d. cholestane

3. **True or False: There are beta-adrenergic receptors in the heart, lungs, liver, vascular smooth muscle, and many other areas of the body.**

    a. True
    b. False

4. **A specific labeled use for _____ includes treatment of dangerous ventricular arrhythmias.**

    a. Esmolol
    b. Propranolol
    c. Labetalol
    d. Sotalol

5. **Cardioselective beta-blockers and beta-blockers with ISA can be used for patients who have**

    a. symptomatic bradycardia.
    b. cardiogenic shock.
    c. mild to moderate asthma or COPD.
    d. decompensated heart failure.

6. **Esmolol, a cardioselective beta-adrenergic blocker, is contraindicated when there is**

    a. hepatic impairment
    b. peripheral vascular disease
    c. sick sinus syndrome
    d. concurrent administration of calcium channel blockers

7. **What conditions are considered to be absolute contraindications to beta-blockers?**

    a. Heart conduction abnormalities
    b. Symptomatic bradycardia
    c. Asthma
    d. Diabetes mellitus

8. **Long-term treatment with beta-blockers could increase decompensation-free survival in patients with clinically significant portal hypertension and**

    a. compensated cirrhosis.
    b. end-stage renal failure.
    c. pheochromocytoma.
    d. cardiogenic shock.

9. **Patients taking certain antidepressants and a beta-blockers can be at risk for adverse events such as _____, particularly in antidepressant drugs which are inhibitors of cytochrome P450 2D6 liver enzymes (CYP2D6).**

    a. exertional angina
    b. hypertension
    c. falls
    d. a hemostatic event

10. **A patient who has asthma or COPD should particularly avoid**

    a. all beta-blockers.
    b. cardioselective (blockade of $ß_1$ adrenoceptors) beta-blockers.
    c. vasculoselective (blockade of alpha adrenoceptors) beta-blockers.
    d. non-selective (blockade of both $ß_1$ and $ß_2$ adrenoceptors) beta-blockers.

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