THE PHARMACY AND WELLNESS REVIEW

An Academic Review of Therapeutics

Legislation Editorial

How can pharmacists make an impact?
The goal of achieving provider status for pharmacists can only be achieved one way: through the collective efforts of the profession. Many pharmacists and pharmacy students are content to let the few champions of the profession lead the charge for the progression of pharmacy, but this approach is no longer sufficient. The pharmacy profession's voice tends to be a quiet one; in order to achieve provider status, it must roar.

All pharmacists and pharmacy students can support the initiative. One simple way to provide your support is to join national and state professional pharmacy organizations; most of these organizations have joined forces to rally for the cause, and your membership is vital to the effort. You can find out more ways to volunteer through your organization as a member, or how to provide financial support to further the effort. You can also give your organization the names of patients or physicians who would be willing to provide testimonials regarding the benefit of pharmacy services.

Another very effective means of advocacy is to engage your congressional legislator; invite them to your practice site to see the benefits of pharmacy services firsthand, or share your own experiences and how your clinical services have impacted patients, physicians, payers and general outcomes. Many lawmakers are unaware of the services pharmacists provide and the extent of the profession's capabilities; simply informing your legislator of these services and the impact pharmacists make can go a long way in advancing the profession.

How to identify/contact your representative
One of the most important actions that pharmacists can take is contacting their elected officials. Senators and congressmen/women have the power to pass the laws that will give pharmacists provider status. It is our responsibility as their constituents to educate them on the positive impact pharmacists with provider status will have on the health care system. With the transitional period our health care system is currently going through, ways to improve health outcomes for constituents have never been more important to our elected officials.

The first step in this process is to identify which officials represent one's district. To locate a congressman/woman, the U.S. House of Representatives has a very easy-to-use Web page at http://www.house.gov/representatives/find/. On this page, constituents only need to enter their zip code, and the corresponding representative will appear. Each representative has a link shaped like an envelope that leads to a contact form. Similarly, at http://www.senate.gov/general/ contact_information/senators_cfm.cfm, constituents can locate their senators and contact forms. These contact forms are a way to explain provider status, but much more importantly they are a gateway to setting up a meeting with the representative. A well-thought-out message to a representative can lead to a critical face-to-face meeting. In-person communication can truly create significant change.

What to talk about with your representative

When contacting your representative, you may do so via letter or by scheduling a visit. It is important to introduce yourself and state your credentials for any initial contact. The representatives want to know who is advocating for the cause and the relation the advocate has with the topic of discussion. If you would like a response, remember to include a return address or offer your email or telephone number. This is especially helpful if the representative has any additional questions or concerns to discuss with you before further legislation takes place.

Remember that the majority of our representatives are not familiar with the pharmacy profession. Make sure to have a good understanding of pharmacist provider status legislation and provide your representative with as much detail as possible. Information may include, but is not limited to, introduction of pharmacy provider status legislation, the average workday of a pharmacist, programs such as medication therapy management and rapid diagnostic/point of care testing that show the quality of pharmacists in the community and specific examples of the type of care provided to patients since pharmacists are the most accessible health care professional. It will be good to explain how pharmacists work now and then how that will change once pharmacists obtain provider status.

Be sure when reaching out to your representative to only talk about one topic at a time, because there will always be other opportunities to contact your representative for additional legislative topics. It is also important to be brief, limiting letters to one page or scheduling a quick 10 to 15 minute visit. Refrain from including personal experiences or feelings toward the subject matter and only discuss the facts. Remember to be courteous to your representatives and their staff, as they are the ones to speak on your behalf when it comes time for legislation. In closing your letter or discussion, thank your representative for his or her time and again offer follow up for any questions with your email or a return address.

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For more information on how to become an advocate of the pharmacy profession, please visit the American Pharmacists Association advocacy website at http://www.pharmacist.com/providerstatusrecognition.

Medication Overdoses in the Emergency Department:
Oral Hypoglycemic Agents, Atypical Antipsychotic Agents, Beta-Blockers, Calcium Channel Blockers, and Digoxin

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

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Objectives
After completion of this program, the reader should be able to:
1. Explain the pathophysiology behind oral hypoglycemic agents, atypical antipsychotic agents, beta-blockers, calcium channel blockers, and digoxin.
2. Describe the presenting symptoms associated with the aforementioned drug classes in an overdose.
3. Discuss recommended treatment options in cases of toxicity.
4. Describe the pharmacist's role in treating toxicological emergencies.

Abstract
The number of medication toxicities has been steadily increasing with more patients presenting to the emergency department for both intentional and unintentional overdoses. Oral hypoglycemics, atypical antipsychotics, beta-blockers, calcium channel blockers and digoxin overdoses are some of the more common medication toxicities health care professionals may see in practice. Toxic doses of oral hypoglycemic agents, beta-blockers, calcium channel blockers and digoxin have more definitive options for treatment, while atypical antipsychotic overdoses are managed with supportive care. Pharmacists in particular play a pivotal role in identifying presenting symptoms and recommending appropriate treatment options in toxicological emergencies.

Introduction
While incidences of toxic exposure to medications may be intentional or unintentional, trends are indicative of a rise in medication overdoses.[1] Emphasis on opioid and prescription analgesic abuse remains a high priority. However, several other medication classes may be overlooked. In 2004, there were upwards of 10,000 cases of oral hypoglycemic overdose used in the treatment of diabetes.[2,3] A significant number of atypical antipsychotic overdoses were reported from 2001 to 2005, some of which ended in fatality.[4] Beta-blockers and calcium channel blockers show a combined incidence of over 30,000 overdoses, 57 of which were fatal.[5,19,20] The cardiac glycoside digoxin has also been associated with severe toxic

events and patient fatalities.[6] Pharmacists, as drug experts, should be aware of toxicity potential for all medications and should be prepared with the knowledge for treatment.

Oral Hypoglycemics
Epidemiology
Type 2 diabetes mellitus (DM2) is a disease on the rise, affecting over 190 million patients in 2006, with a projected population of over 325 million by 2025.[3] In the attempt to treat DM2, the use of oral hypoglycemics has steadily risen with the disease prevalence. A variety of medication classes are available including sulfonylureas, biguanides, meglitinides, thiazolidinediones and alpha-glucosidase inhibitors. While such therapy choices are appropriate for controlling blood glucose levels in the insulin-resistant patient, several of these classes have been shown to reach toxic levels, thereby causing severe adverse effects. Biguanides, for example, accounted for 40 percent of the 10,000+ cases, as did sulfonylureas; a majority of which were seen in children.[2,3]

Mechanism
As there are several classes of oral hypoglycemics, it is important to make distinctions by which their mechanisms work so that toxic levels can be more readily identified and treated. Sulfonylureas work by lowering potassium channel permeability in pancreatic beta cells, leading to release of intracellular calcium and release of insulin-containing granules. The result is a lowered threshold at which insulin will be secreted in the presence of glucose.[7] It should be noted that the second generation sulfonylureas, including glyburide, glipizide, and glimepiride, have a shorter half-life ($t_{1/2}$) and duration of action (DOA).[2] Meglitinides work similarly in lowering the potassium channel permeability allowing for intracellular calcium to depolarize pancreatic beta cells.[8] By stimulating the Peroxisome Proliferator Activated Receptor-gamma (PPAR-gamma) in adipose, skeletal muscle, and liver tissue, thiazolidinediones promote the expression of glucose controlling genes in the presence of insulin.[9] In order to increase insulin sensitivity, biguanides will increase the ability to metabolize glucose, and decrease glycogenolysis, the breakdown of glycogen to form glucose.[10] Alpha-glucosidase inhibitors will slow the enzymatic breakdown of carbohydrates, thereby lowering the rise in post-prandial blood glucose levels. By this process, glycosylated hemoglobin will be decreased.[11] In recognizing the basic mechanisms for the varying classes of oral hypoglycemics, identifying appropriate treatment becomes more clear.

Presenting Symptoms of Toxicity
Upon over-ingestion of oral hypoglycemics, patients will tend

to have similar presentations, yet the specific drug class will be distinguishable upon the presence of unique symptoms. As could be expected, patient presentation is associated with a hyperinsulinemic/hypoglycemic state. In sulfonylurea toxicity, for example, it is common to see neuroglycopenia (glucose deficiency in the brain), coma and seizures, all associated with low glucose levels. Additionally, counter-regulatory hormone effects in response to the low glucose may induce diaphoresis and tachycardia.[3,7] An acute state may occur in as little as one to eight hours, where a chronic toxicity may be delayed over several days.[3] Meglitinides will present similarly to sulfonylureas, however, they are associated with a quicker onset of action (30 minutes versus one to eight hours) in an acute situation.[3]

Patients with increased levels of thiazolidinediones will show no acute symptoms of toxicity, as they are dependent on the presence of insulin to exert their effects. In a chronic overdose, there would be an elevation of transaminases as well as alkaline phosphatase levels, indicating hepatic toxicity. Also associated with thiazolidinediones is an increased prothrombin time (PT) and international normalized ratio (INR), in addition to the expected hypoglycemic sequelae such as bradycardia, coma and hypotension.[3]

Biguanides are unique in that they have the potential to cause lactic acidosis. It is common for patients with overdoses (or even as side effects in normal doses) to present with gastrointestinal (GI) discomfort, abdominal pain, nausea, vomiting and diarrhea. Alongside tachypnea, hypotension, hypothermia and confusion (commonly associated with hypoglycemia), it is possible to see renal failure and cardiovascular effects such as ventricular arrhythmias and vascular resistance with biguanides.[3]

Diagnosis and Treatment
While no single test may be used to diagnose a patient presenting with oral hypoglycemic toxicity, a combination of subjective and objective information may be used to assess an individual's status. There are many common presenting symptoms such as hypoglycemia, and some distinct tests that set drug classes apart. For example, liver function tests may be appropriate for suspected thiazolidinedione toxicity, or arterial blood gas levels in the instance of biguanides. Timeline may also be a factor in determining the class of drug, whether the onset was acute such as with some sulfonylureas, or chronic, which is more commonly associated with thiazolidinediones.

In treating the sulfonylurea and meglitinide classes, it is important to first give the patient quickly metabolized carbohydrates in the form of oral glucose or intravenous (IV) dextrose. A 50 mL bolus of 50 percent dextrose (D50W) and dextrose containing IV fluids should be administered.[3,12,13] The possibility for recurrent hypoglycemia exists in which the pancreas will release insulin in response to the IV dextrose. Upon refractory hypoglycemia, use of alternative therapy is required.[13] The second option for sulfonylurea-induced hypoglycemia is octreotide, a somatostatin analog that inhibits glucagon and insulin secretion.[14] By binding to somatostatin-2 receptors on pancreatic beta cells, it inhibits G-protein coupled voltage gated calcium channels from being opened. This inhibition of calcium influx will stop further insulin release by pancreatic beta cells.[13] Octreotide is U.S. Food and Drug Administration (FDA) approved for the treatment of various endocrine related disease states such as acromegaly and pancreatic tumors; however, it has not been FDA approved as an antidote for sulfonylurea toxicity.[13,14] Subcutaneous and intravenous routes of administration have equivalent bioavailability with peak effects occurring after 30 minutes. Adult dosing of octreotide ranges from 50 to 100 mcg subcutaneously every six to 12 hours, while pediatric dosing requires 1 to 2 mcg/kg up to 50 mcg every six to 12 hours.[13] Glucagon may also be used for the treatment of sulfonylurea overdose, as it will promote the breakdown of glycogen and synthesis of glucose to combat low glucose levels.[13] Glucagon, however, may also influence the release of insulin.[13] Studies were not found to provide evidence of glucagon or octreotide as effective treatment options in meglitinide overdose. Activated charcoal will bind to meglitinide entities and is most effective early on in treatment.[3]

In the instance of lactic acidosis with excess biguanide ingestion, the primary goal in treating the patient is acid-base restoration, which can be achieved with the use of sodium bicarbonate (1-2 mEq/kg). Activated charcoal may be administered to the patient, even late in an overdose, as biguanides will still be present in the gastrointestinal tract. In an emergency situation where renal function is critically impaired, hemodialysis may be initiated alongside sodium bicarbonate.[3]

Thiazolidinediones, which are known to cause hepatic toxicity, are most appropriately treated with drug discontinuation.[3] Neither pioglitazone or rosiglitazone were found to be dializyzable through either conventional (coefficient of ultrafiltration <8 mL/hour/mm), high permeability (coefficient of ultrafiltration >8 mL/hour/mm) or peritoneal dialysis.[15]

Atypical Antipsychotics
Epidemiology
Atypical antipsychotic medications, including clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole, have become widely popular in treating schizophrenia and related psychiatric disorders. These drugs have a more favorable adverse effect profile compared to the traditional antipsychotics, contributing to their preference over other medications. However, overdose of antipsychotic medications is common, and in rare cases even fatal. From 2001 to 2005, 156,431 ingestions were reported to the Toxic Exposure Surveillance System (TESS), an organization maintained by the American Association of Poison Control Centers.[4] Of the 156,431 cases reported, 8,894 had major effect outcomes and 403 resulted in death.[4] Total fatalities to date due to atypical antipsychotic drug overdose are unknown.

Mechanism
Atypical antipsychotic medications are tricyclic dibenzothiazepines that have unique receptor binding affinities and more favorable side effect profiles. The atypical agents are

defined clinically as having minimal or no extrapyramidal symptoms at appropriate therapeutic doses and have less potential to cause tardive dyskinesias and elevation of serum prolactin concentrations.[4,16] Atypical antipsychotics are dopamine D_2 receptor antagonists and serotonin $5HT_{2A}$ receptor antagonists. The decreased incidence of extrapyramidal side effects is attributed to the decreased affinity of the atypical antipsychotics to the D_2 receptor. The "negative" symptoms of schizophrenia, including avolition, anhedonia, alogia and social withdrawal, are alleviated due to the drugs' $5HT_{2A}$ antagonistic activity.[4,16] However, aripiprazole differs from other atypical antipsychotics because it is a partial agonist at the D_2 and $5HT_{1A}$ receptors and an antagonist at the $5HT_{2A}$ receptors.[4] Typical side effects that would be expected of these drugs include orthostatic hypotension due to α-adrenergic receptor blockage, sedation, sinus tachycardia and urinary retention (associated with clozapine, olanzapine, quetiapine).[16]

Presenting Symptoms of Toxicity
Toxic doses in patients are highly variable because an overdose may occur at therapeutic or supratherapeutic doses. The most serious presenting symptoms involve the central nervous system (CNS) and cardiovascular system. A patient may present with pronounced sedation, most common with clozapine and quetiapine, due to blockade of CNS histamine H_1 receptors. Tachycardia, mild hypotension and QT prolongation may also be present. Another serious and potentially fatal symptom of overdose is neuroleptic malignant syndrome (NMS) which is characterized by hyperthermia, autonomic instability, neuromuscular rigidity and altered mental status.[16] Patients will most likely seem agitated, have muscular rigidity and may present with additional extrapyramidal effects such as bradykinesia and tremor.[16] Lastly, antimuscarinic delirium may also be present in toxicity due to antagonism of central and peripheral muscarinic receptors. Antimuscarinic delirium is most commonly seen with clozapine, olanzapine and quetiapine, and less often seen with risperidone, ziprasidone and aripiprazole. Presenting symptoms of antimuscarinic delirium that may suggest overdose include: hyperthermia, tachycardia, blurred vision, flushed dry skin, absent bowel sounds, urinary retention, agitation, hallucinations, mumbling speech and repetitive picking behavior.[16]

Diagnosis and Treatment
Diagnosing an overdose caused by atypical antipsychotics is primarily supported by gathering information in the patient's clinical history, physical examination and presenting symptoms. Obtaining serum concentrations of antipsychotics is not helpful in guiding therapy because data listing toxic serum concentrations are not widely available and the concentrations are not definitively correlated with clinical signs and symptoms.[17] Routine urine screens of commonly abused drugs do not detect antipsychotics and therefore are not helpful in managing toxic cases.[16]

Co-ingestion of other medications is common in overdose, especially with other psychotropic agents such as antidepressants, sedatives, hypnotics, anticholinergics, valproic acid and lithium.[17] Co-ingestion of nonprescription analgesics such as acetaminophen and aspirin are also common. Obtaining a serum concentration of acetaminophen and salicylates should be considered in all toxic cases.[16,17]

Supportive therapy is the cornerstone of treatment for patients with antipsychotic overdose. Use of supplemental oxygen in hypoxic cases and administration of thiamine and parenteral dextrose in altered mental status patients are typical first-line therapies in managing overdoses. All patients who are symptomatic should be continuously monitored for cardiac abnormalities and have an electrocardiogram (ECG), particularly focusing on QT prolongation. Moreover, serum electrolytes should be monitored and corrected, as hypokalemia and hypomagnesemia could exacerbate QT dysrhythmias. Hypotension due to peripheral alpha 1-blockage can be corrected using intravenous fluids. If required, vasopressors of choice include alpha-agonists, norepinephrine or phenylephrine.[16]

Gastrointestinal decontamination procedures are rarely necessary with antipsychotic overdoses. Activated charcoal (1 g/kg by mouth or nasogastric tube) can be considered in a large or multi-drug overdose within an hour of ingestion as long as the patient does not present with sedation or vomiting.[16,17] While the administration of activated charcoal is time sensitive, the antimuscarinic effects and slowed gastric emptying caused by the antipsychotic may improve the beneficial effects of activated charcoal.

Pronounced anticholinergic symptoms are common with atypical antipsychotics. The cholinesterase inhibitor physostigmine has been used successfully in overdosed patients, particularly in improving agitated delirium. Physostigmine should be given in 0.5 mg increments every three to five minutes under close patient observation.[17] Other cholinesterase inhibitors such as edrophonium, neostigmine and pyridostigmine should not be used to improve anticholinergic delirium because these drugs do not cross the blood-brain barrier.[17]

Beta-Blockers and Calcium Channel Blockers
Epidemiology
Beta-blockers (BB) and calcium channel blockers (CCB) are used to treat various medical conditions such as hypertension, angina pectoris, supraventricular tachycardias, tremors, anxiety and others. According to the American Association of Poison Control's 2007 records, 10,084 exposures to CCBs were reported, of which 435 were classified as moderate to major toxicity and 17 exposures resulted in death.[18] The National Poison Data System (NPDS) reported nearly 20,000 exposures to BBs in 2007, of which 200 to 400 cases were classified as major toxic events with over 40 deaths.[18,19] Interestingly, propranolol accounts for a majority of self-induced poisonings, which may be attributed to its use in treating anxiety, stress and migraine patients.

Mechanism
Although BBs and CCBs have differing mechanisms of action, both are involved in interfering with calcium flux across cell

membranes. Cardiovascular function is dependent on calcium flow across cell membranes to regulate cardiac automaticity, myocardial conduction and contraction, vascular tone and insulin secretion.

Beta-blockers selectively antagonize β-adrenergic receptors that are linked to G_s proteins. Three subtypes of the β-receptor are known: $β_1$-receptors regulate myocardial tissue and effect rate of contraction, $β_2$-receptors regulate smooth muscle tone and influence vascular and bronchiolar relaxation and $β_3$-receptors are thought to effect lipolysis with some influence on cardiac inotropy.[20] Under normal conditions, these G_s proteins stimulate the increase of intracellular cyclic adenosine monophosphate (cAMP) with subsequent increase of calcium flow through L-type calcium channels and release of calcium from the sarcoplasmic reticulum. The increase in intracellular calcium is directly proportional to the overall strength of contraction brought on by the interaction between actin and myosin. Beta-blockers competitively inhibit β-receptors, therefore indirectly decreasing cAMP production and intracellular calcium levels. This mechanism results in decreased cardiac automaticity, slowed conduction and decreased contractility.[20] Over 15 BBs are on the market today, many of which have variable selectivity for β-receptor subtypes and fewer which have α-receptor antagonistic activity, also referred to as intrinsic sympathomimetic activity. Other properties of individual BBs that are important to note in toxic cases are the lipid solubility and sodium channel blocking activity.[21] Highly lipophilic agents, such as propranolol, can cross the blood-brain barrier resulting in CNS effects.

Calcium channel blockers have the same overall pharmacological result as beta-blockers with a slight difference in mechanism. CCBs directly inhibit calcium influx by blocking voltage-gated L-type calcium channels located in myocardial cells, smooth muscle cells and β-islet cells of the pancreas. Two types of CCBs are known and exhibit different selectivity for cardiac versus vascular channels. The dihydropyridine (DHP) CCBs, which include amlodipine and nifedipine, preferentially act on peripheral vasculature. Antagonism of calcium channels in the peripheral vasculature results in decreased coronary vascular resistance, increase in coronary blood flow and overall vasodilation. Verapamil and diltiazem make up the non-dihydropyridine (Non-DHP) CCBs that are somewhat less selective and target both cardiac tissue and peripheral vasculature. The results of the non-dihydropyridines acting in cardiac tissue include decreased nodal conduction and decreased myocardial contractility. Moreover, decreased insulin secretion is an outcome of CCB activity in the pancreas.

Presenting Symptoms of Toxicity
Patients experiencing toxic doses of either BBs or CCBs may present with symptoms within two to three hours of ingestion. Immediate-release preparations develop toxicity within six hours and toxicity from sustained-released products may be delayed for six to 12 hours.[18,19] In general, toxicities usually present as an extension of the drug's therapeutic effects. Specifically, bradycardia and hypotension caused by myocar-

dial depression and peripheral vasodilation are expected.[20] Early or mild symptoms may include dizziness, fatigue and lightheadedness that may manifest as lethargy and altered mental status. Common ECG findings during BB toxicities are first-degree atrioventricular (AV) block and interventricular conduction delays; ECG findings for CCB toxicities are sinus bradycardia, AV blocks, complete heart block, junctional rhythm and QT prolongations.[19,20]

While the clinical manifestations for BB and CCB overdose are similar, there are subtle differences that may suggest poisoning in one class over the other. Hyperglycemia is expected to present more with CCBs, particularly with serious verapamil, diltiazem and DHP overdoses, whereas hypoglycemia is common in BB toxicity.[20] Mild hypokalemia and hypocalcemia have been reported in CCB overdose, but are not reliable differentiating factors. CCB toxicity can lead to hypoperfusion and end-organ ischemic complications such as non-cardiogenic pulmonary edema, seizures, myocardial infarction and renal failure.[20] Beta-blocker toxicities can also have dangerous complications such as rhabdomyolysis, renal failure, seizures and bowel infarction.[19]

Diagnosis and Treatment
Diagnosing toxicities due to BBs and CCBs is primarily supported by clinical manifestations, continuous cardiac monitoring with an ECG and serum glucose concentrations. While obtaining serum glucose concentrations is not definitively diagnostic, this value may warrant further treatment. In reported cases, patients who required vasopressors, a pacemaker or who died of overdose had an initial mean serum glucose concentration of 188 mg/dL compared to an average of 122 mg/dL in those not requiring intervention.[18,19] These findings may be useful in determining the initial severity of toxicity.

Managing BB and CCB overdoses can be accomplished in a similar manner, as their mechanisms are physiologically comparable. Pharmacological therapies will be discussed in further detail in the following paragraphs. When toxicity is suspected through clinical manifestations, an ECG should be obtained and repeated every one to two hours, along with attention to airway, breathing and circulation. Supplement oxygen as clinically necessary and obtain intravenous access.[18-20] Initial resuscitation fluid bolus with 10 to 20 mL/kg of intravenous crystalloids, likely normal saline, is recommended for hypotensive patients, however be aware that poisoning may produce drug-induced inotropic failure, making fluid overload a concern.[18-20] Gastrointestinal decontamination is recommended to prevent delayed cardiovascular toxicity, especially with CCBs. Multiple-dose activated charcoal (MDAC) is recommended ideally within one hour of ingestion at an initial dose of 1 g/kg followed by 0.5 g/kg if the patient shows signs of continuing absorption. Whole-bowel irrigation (WBI) should be used in the presence of suspected overdose with sustained-release CCBs. Whole-bowel irrigation with polyethylene glycol solution at 1 to 2 L/h orally or via nasogastric tube is recommended and should be continued until the rectal effluent is clear.[18]

Pharmacological Treatments

Atropine

Atropine is an initial treatment of choice to be administered in patients with symptomatic bradycardia. Although atropine was ineffective in improving heart rate in clinical cases of CCB overdoses, atropine should still be considered based on its availability and familiarity. Doses can be administered at 0.5 to 1 mg IV every two or three minutes up to a maximum dose of 3 mg.[18] In severely poisoned patients, treatment failure with atropine is expected, however initial treatment with calcium may improve the efficacy of atropine.

Catecholamines

Catecholamines are administered to act as agonists at β_1-adrenergic receptors in the myocardium or at α_1-adrenergic receptors in the peripheral vascular smooth muscle in order to improve heart rate, contractility and peripheral vasoconstriction. However, the effects of catecholamines on β-adrenergic receptors may be blunted due to the excessive β-receptor blockage from the drug overdose. No single agent has been proven to be consistently effective in all clinical cases due to the variability of the patient and involved receptors.[18] Epinephrine has shown to improve heart rate and blood pressure the most and is a reasonable choice for either a BB or CCB overdose. Dopamine and norepinephrine are also logical choices; especially in CCB toxicities.[18] Using a combination of inotropes and vasopressors will most likely be necessary.

Calcium

Calcium is a logical treatment option for BB and CCB toxicity with the intention of increasing extracellular calcium, allowing calcium influx through unblocked L-type channels. Calcium ions can correct the negative inotropy, delayed conduction, and hypotension in poisoned patients, but have a limited effect on heart rate.[20] Ideal doses of calcium are not yet established, but the attention and selection of a specific calcium salt is critical for dosing. Calcium chloride contains three times the amount of elemental calcium as calcium gluconate and is therefore preferred, although there is no difference in efficacy.[18-20] Literature suggests initial intravenous infusion of approximately 13 to 25 mEq of calcium over five minutes, which equates to 10 to 20 mL of 10 percent calcium chloride or 30 to 60 mL of 10 percent calcium gluconate. The initial infusion can be followed by either repeat boluses every 15 to 20 minutes up to three or four doses or a continuous infusion of 0.5 mEq/kg/hr of calcium.[18] It is important to note that calcium chloride has a high potential to cause tissue damage if extravasated, therefore it is best if administered through a central venous catheter.[20]

Glucagon

Glucagon is the therapy of choice in BB overdose because it has both inotropic and chronotropic effects independent of activating β-adrenergic receptors. Ideal doses of glucagon are not yet established and maximum doses are undefined. An appropriate starting dose is a bolus of 5 to 10 mg (150 mcg/kg) over one to two minutes followed by a continuous infusion of 2 to 10 mg/hour once a response occurs.[20] The glucagon infusion could also be started at the "response dose,"

which means the hourly infusion rate is set equal to the initial cumulative dose required to obtain a response. Because nausea and vomiting can occur with bolus doses of glucagon over 50 mcg/kg, airway protection is necessary to prevent aspiration.[19] Hyperglycemia and mild hypocalcemia can also be expected and should be treated appropriately.

Hyperinsulinemia Euglycemia

Hyperinsulinemia euglycemia (HIE) therapy has become particularly more prominent in the treatment of CCB toxicity, but is also clinically used in BB overdose.[19] Insulin facilitating myocardial utilization of carbohydrates is the foundation for the theory behind using insulin in treating BB and CCB overdose. Under healthy conditions, myocardial tissue relies on free fatty acids to fuel its metabolic needs. Drug poisoning shifts its need to be more carbohydrate dependent.[22] Toxic levels of BBs and CCBs also inhibit calcium-mediated insulin secretion from the β-islet cells in the pancreas, therefore myocardial cells become dependent upon concentration gradients for glucose uptake rather than insulin-mediated active transport.[20,22] Studies involving verapamil toxicity showed improved glucose uptake with insulin administration and consequently improved contractility. Again, ideal doses have not been established but typical therapy begins with a bolus of 1 unit/kg of regular human insulin with 25 to 50 mL of D50W IV, followed by insulin infusion 1 units/kg/hr and dextrose infusion at 0.5 g/kg/hr.[20,22] Glucose should be monitored every 30 minutes for the first four hours and titrated to maintain euglycemia. A response to HIE therapy may be delayed for 15 to 60 minutes. It is also important to monitor glucose and electrolyte levels for several hours after insulin is discontinued.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors (PDIs) such as amrinone and milrinone are typically used as second-line agents in BB and CCB toxicity. Phosphodiesterase inhibitors inhibit the breakdown of cAMP by phosphodiesterase, thereby increasing cAMP concentrations, increasing intracellular calcium and improving inotropy. Case reports suggest an initial bolus dose of 1 mg/kg of amrinone over 2 minutes followed by a continuous infusion of 5 to 20 mg/kg/min.[18]

Phosphodiesterase inhibitors have been clinically successful when used in combination with another inotrope, such as glucagon.[18] Glucagon stimulates cAMP production while PDIs inhibit its breakdown, increasing the overall effects of cAMP. However, PDIs nonselectively inhibit phosphodiesterase in the vascular smooth muscle, causing smooth muscle relaxation, peripheral vasodilation and hypotension. The nonselective behavior of PDIs makes it a second-line agent and should only be used in patients who have hemodynamic monitoring, as the additive hypotension could be dangerous in BB and CCB poisoning.[18,20]

Methylene Blue

Methylene blue (MB) is an experimental antidote for refractory vasodilatory shock from dihydropyridine overdoses, particularly amlodipine. Methylene blue is thought to interfere with guanylate cyclase activity and endothelial nitric

oxide synthase activity, preventing the cGMP production and vasodilation effects of amlodipine.[23,24] Literature that supports the use of MB in refractory vasodilatory shock is limited to retrospective case reports.[23] Patients in two case reports were administered MB 14 and 16 hours post ingestion. They received 2 mg/kg IV of MB over 20 minutes followed by 1 mg/kg/hr after not responding to normal saline, calcium gluconate, glucagon, dopamine, norepinephrine and high-dose insulin euglycemia therapy.[23,24] One hour after MB administration, the case patients responded with an elevation in blood pressure and heart rate.[23,24] Clinically, methylene blue may be a newer option for antidotal treatment of vasodilatory shock from dihydropyridine overdoses, however the literature is limited to use in amlodipine overdoses and no ideal doses of MB have been established.

Digoxin
Epidemiology
An estimated 4 to 5 percent of digoxin users per year experience toxicity.[25] In 2011 alone, there were 2,513 reported exposures to cardiac glycosides resulting in toxicity. The majority of cases were the result of an adverse event with prescribed use of a cardiac glycoside. Of the reported exposures, the majority of cases were classified as being moderately severe in nature, with 27 cases resulting in death.[6] Each of these incidents is estimated to have cost the U.S. health care system between $1,500 and $6,500.[25]

Mechanism
Cardiac glycosides as a class exhibit their function by inhibiting the Na^+/K^+ ATPase in myocytes. Pump inhibition will cause an increase in sodium concentration within the cell.[26,27] This results in an increase in the resting membrane potential of the myocyte, allowing voltage-gated calcium channels to open and triggering calcium release from the sarcoplasmic reticulum.[26] Additionally, the Na^+/Ca^{2+} exchange pump will be affected by the change in sodium's electrochemical gradient, thus inhibiting its ability to drive calcium from the cell. The overall increase in intracellular calcium concentration results in positive inotropy.[27]

In a toxic situation, the high sodium levels can cause phase IV depolarization to lengthen and increase the resting membrane potential. This allows cardiac cells to fire off their own action potential, and may lead to the development of arrhythmias.[28]

Presenting Symptoms of Toxicity
In addition to heart arrhythmias, toxic effects may be observed in other organs throughout the body due to the presence of Na^+/K^+ ATPase pumps in a multitude of cells. Symptoms caused by digoxin toxicity include gastrointestinal issues, such as nausea, vomiting, and anorexia, and neurological symptoms, including confusion, disorientation, lethargy, delirium, weakness, and vision disturbances.[25,26,28] Chronic toxicity is typically observed in practice.[6] These patients more frequently exhibit neurological symptoms than those suffering from acute overexposure, who commonly demonstrate the gastrointestinal side effects. In either situation, an ECG, may illustrate extrasystoles, ST depression, and minor degrees of AV node block, among other issues.[28]

Diagnosis and Treatment
It is important for pharmacists to be able to recognize and properly treat patients that are exhibiting symptoms of digoxin toxicity, as treatment should be provided as soon as possible. Although acute cases of toxicity may occur, in which a patient may ingest excessive amounts of digoxin at one time, most patients with digoxin toxicity experience chronic toxicity. In this instance, adverse events are exhibited after multiple ingestions of the medication, during which the digoxin accumulates as a result of impaired drug clearance. As such, there is a gradual increase in serum digoxin concentration until toxic levels are achieved. Thus, serum digoxin levels may be beneficial, but should be obtained after six hours of ingestion to avoid misleading results in cases of acute ingestion.[26] If the overdose is known to be acute and has occurred within two hours, cleansing the gastrointestinal system through the use of multiple doses of activated charcoal may be a valid option.[26,28] Gastric lavage should be utilized with care, as it may worsen cases of bradycardia. Additionally, if a patient is experiencing hypokalemia, this condition should be corrected.[28]

Treatment options for the patient's arrhythmia will be dependent upon how the patient is displaying, so this must be treated on an individual basis.[26] High levels of potassium will hinder digoxin binding to the Na^+/K^+ ATPase, and therefore may be useful in treating mild cases of overexposure.[26,28] It should also be noted that hyperkalemia can be problematic to the patient's health, and should be monitored.[28]

First-line therapy, when available, is Digoxin-Fab. This medication is a highly utilized treatment method that functions as a specific digoxin-binding antibody, thus decreasing the amount of free digoxin to bind to the Na^+/K^+ ATPase. Digoxin-Fab is indicated in both acute and chronic toxic emergencies.[29] The onset of action is reported to occur in less than 30 minutes.[29] A 40 mg vial of Digoxin-Fab will bind approximately 0.5 mg of ingested digoxin.[25] Therefore, the required dose of Digoxin-Fab is dictated by the amount of consumed digoxin that must be nullified.[28] Health care professionals should remember that any time this drug is utilized, there is the potential of developing a severe immunological reaction to the administered antibodies. Immune responses to the antidote should be closely monitored.[30]

In an acute crisis where an unknown amount of digoxin has been ingested, 20 vials are typically sufficient for treatment. They may be administered either all at once as a single dose or divided into two equal doses. In the case of dividing into two equal doses, one dose is administered and the patient's response is monitored to determine if the other half is required.

In an acute situation in which the amount of consumed digoxin is known, the corresponding dose of Digoxin-Fab can be calculated. Initially, the total body load of consumed digoxin should be determined using one of the following equations, depending upon the prepared formulation of digoxin:

Total body load (mg) = Total amount of digoxin **capsules** consumed (mg)

Total body load (mg) = Total amount of digoxin **tablets** consumed (mg) x 0.8

Once the value for total body load has been found, the number of vials of Digoxin-Fab that are necessary can be calculated as follows:

Digoxin-Fab required for treatment (mg) = Total body load (mg) / 0.5

Vials of Digoxin-Fab to be used = Digoxin-Fab required for treatment (mg) / 40 mg/vial

In this manner, the math can quickly be completed to determine the appropriate way to treat an overdose patient.[29] The pharmacist must utilize care in these situations, however, due to the possibility of unreliable patient accounts regarding the amount of drug ingested.[30]

In a situation involving chronic overexposure, six vials is usually adequate to treat a patient.[29]

Calcium is typically contraindicated in patients suffering from digoxin toxicity, because an excess of calcium can throw the heart into a non-contractile state as a result of overstimulation. This is sometimes known as a "stone heart" state. Despite this, calcium is sometimes desired in the treatment regimen to counteract the patient's hyperkalemia. In a recent retrospective observational study conducted by Levine and colleagues, patient outcomes were evaluated in cases of digoxin toxicity in which calcium treatment was utilized. Overall mortality between both those who received calcium and those who did not were similar.[27] These findings suggest that calcium may not be harmful in digoxin overdose situations, and that the health care practitioner must use professional judgment when considering calcium as a treatment option to combat hyperkalemia.

Supportive care should be provided for the patient in addition to one or more of the above treatment methods. This will provide the patient with the best possible odds of surviving the digoxin overdose with minimal lasting effects.

Role for Pharmacists

Toxicity can be the result of acute or chronic exposure, and may be either intentional or unintentional. In any scenario, pharmacists play a vital role in the health care team by helping to select, properly dose and oversee drug treatments. This becomes especially important in many of the previously listed cases, in which treatment strategies may include multiple drugs and may require monitoring various parameters in order to properly care for the patient.

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Assessment Questions

1. Pronounced anticholinergic symptoms are common with atypical antipsychotic toxicity. What intervention can be used to manage these symptoms, especially agitated delirium?
   A. Physostigmine
   B. Edrophonium
   C. Neostigmine
   D. Pyridostigmine

2. How is an atypical antipsychotic overdose primarily diagnosed?
   A. By obtaining serum concentrations of the drug
   B. Collecting and analyzing patient's clinical history, physical examination, and presenting symptoms
   C. Conducting urine screens
   D. Monitoring changes in the ECG

3. A patient suffering from an atypical antipsychotic overdose typically presents with symptoms involving what system(s)?
   A. Cardiovascular
   B. Gastrointestinal
   C. Central nervous system
   D. A & C
   E. All of the above

4. What is the therapy of choice in treating beta-blocker toxicity?
   A. Atropine
   B. Glucagon
   C. Calcium
   D. Catecholamines

5. What is unique about the presentation of biguanide toxicity compared to other oral hypoglycemics?
   A. Elevated transaminases and alkaline phosphatase
   B. Hypoglycemia
   C. Lactic acidosis
   D. No acute symptom onset

6. Thiazolidinediones do not present with acute symptoms of toxicity because…
   A. They are considered to be a safer class of drugs
   B. They have a very short $t_{1/2}$
   C. They have very low bioavailability upon oral ingestion
   D. They require the presence of insulin to exert their effects

7. In treating the sulfonylurea and meglitinide classes, it is important to first give the patient
   A. Normal saline solution continuous IV
   B. Octreotide 50-100 mcg subcutaneously every 6-12 hours
   C. Quickly metabolized carbohydrates in the form of oral glucose or IV dextrose
   D. Sodium bicarbonate 1-2 mEq/kg

8. In the early stages of _____ toxicity, _____ may be administered because of the medication's tendency to remain in the gastrointestinal tract.
   A. Biguanide, Activated charcoal
   B. Thiazolidinedione, Sodium bicarbonate
   C. Thiazolidinedione, Octreotide
   D. Biguanide, Octreotide

9. JR, a 35-year-old male, arrives in the emergency room complaining of nausea and vomiting. It is determined that he has acute digoxin toxicity. He states that he has swallowed fifteen 25 mg tablets of digoxin. How many vials of Digoxin-Fab will JR likely need for treatment?
   A. 8 vials
   B. 15 vials
   C. 19 vials
   D. 22 vials

10. What ion is associated with "stone heart" state in digoxin toxicity?
   A. Sodium
   B. Potassium
   C. Magnesium
   D. Calcium

To receive continuing education credit for this program, you must answer the above questions and fill out the evaluation form. Please visit www.onu.edu/pharmacy to enter the required information. Please allow two to three weeks for electronic distribution of your continuing education certificate, which will be sent to your valid email address in PDF format.

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Program Title: **Medication Overdoses in the Emergency Department: Oral Hypoglycemic Agents, Atypical Antipsychotic Agents, Beta-Blockers, Calcium Channel Blockers, and Digoxin**
UAN: 0048-0000-14-197-H01-P   CEUs: 0.1

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.

Name:

Address:

City: **State:**   **Zip:**

Phone: **Email:**

Pharmacy License #:   **State:**   **ONU Alumni?**   Y   N

Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals and objectives:					
Explain the pathophysiology behind oral hypoglycemic agents, atypical antipsychotic agents, beta-blockers, calcium channel blockers, and digoxin.	1	2	3	4	5
Describe the presenting symptoms associated with the aforementioned drug classes in an overdose.	1	2	3	4	5
Discuss recommended treatment options in cases of toxicity.	1	2	3	4	5
Describe the pharmacist's role in treating toxicological emergencies.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

_____

_____

_____

Thank you!
Answers to Assessment Questions—Please Circle Your Answer

1. A B C D   4. A B C D   7. A B C D   10. A B C D

2. A B C D   5. A B C D   8. A B C D

3. A B C D E   6. A B C D   9. A B C D

Neonatal Abstinence Syndrome:
A Targeted Review for Pharmacists

Andrew Skouby, fifth-year pharmacy student from Mentor, Ohio; Gabi Gegenheimer, fourth-year pharmacy student from Upper Arlington, Ohio; Kelsey Lindsley, fourth-year pharmacy student from Port Clinton, Ohio; Sarah Kradel, fifth-year pharmacy student from McMurray, Pa.; **Michael Rush**, PharmD '05, CDE, BCACP, Director of ONU HealthWise, assistant clinical professor of pharmacy practice

This knowledge-based activity is targeted for all pharmacists and is acceptable for .5 hour (.05 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-14-192-H01-P

Objectives
After completion of this program, the reader should be able to:
1. Explain the etiology, patient presentation and diagnosis of neonatal abstinence syndrome (NAS).
2. Describe perceived complications of NAS.
3. Describe nonpharmacologic treatment options for treating NAS.
4. List pharmacologic treatment options for opioid exposed NAS, as well as benefits and limitations for each medication.
5. Identify several ways that a pharmacist can impact the care of a patient with NAS.

Abstract
Neonatal abstinence syndrome (NAS) is a disease that impacts drug-exposed infants and describes an array of issues that arise in newborns just hours after birth. Patient presentation and disease symptomatology vary widely based upon the specific substance utilized by the mother while pregnant and duration of exposure. Treatment is dependent on which symptoms are present and, assuming an opioid-derived abstinence syndrome, is based primarily on opioid supplementation to prevent symptoms of withdrawal. Treatment of non-opioid derived abstinence syndrome is often slightly more complex and involves the use of different agents depending on the drug of exposure. Due to the intricate nature of treating NAS, a team of health care professionals, including a pharmacist, should oversee management of the disease state. Pharmacists in both the inpatient and outpatient settings are in important locations to prevent and/or positively impact the outcomes for NAS.

Disease Overview
Neonatal abstinence syndrome (NAS) is a condition that affects drug-exposed infants and encompasses a group of problems that occur in a newborn exposed to illicit or prescription drugs prior to birth.[1,2] Of those children born each year, 3 percent are exposed to illicit or prescription drugs in utero, with 55 to 94 percent of drug-exposed infants displaying symptoms at birth.[2] The disruptive symptomatology of this condition is due to the neonate becoming dependent on substances that cross the placental barrier in utero.[1] Most newborns with NAS will show signs of withdrawal 24 to 48 hours after birth; unfortunately, there is no known way to detect NAS prior to birth.[3]

Patient Presentation
Symptoms of NAS are most commonly due to *in utero* opioid exposure. However, there are a multitude of other implicated medications, including amphetamines, barbiturates, benzodiazepines, cocaine and marijuana, that could also cause NAS.[1] Drug withdrawal symptoms are dependent on various factors such as the type of drug used, the mother's ability to metabolize medications, the amount of drug used and the duration of use.[1] Such factors lead to varying severity of presentation in neonates, including neurological excitability, autonomic dysfunctions, and gastrointestinal (GI) irritability.[4] Examples of such symptoms consist of blotchy skin, diarrhea, consistent crying, fever, hyperactive reflexes, increase in muscle tone, irritability, rapid breathing, seizures, sleep issues, difficulty in weight gain, sweating, tremors and vomiting.[1] Additional signs of NAS include cyanosis, jaundice, hypothermia, electrolyte abnormalities, renal impairment and atrial septum defects.

Diagnosis
Health care providers (most often nurses) can utilize several assessment-based systems in order to determine whether the neonate is displaying withdrawal symptoms. Tools often utilized for analysis include the Finnegan NAS scoring system, a toxicology screening of bowel movements, looking for meconium, and urinalysis.[1] The Finnegan NAS scoring system is an objective evaluation of the central nervous system (CNS), metabolic, motor, respiratory and GI disturbances in children with suspected NAS, assigning numeric values. Those newborns with a score of greater than or equal to eight on two or more Finnegan NAS scoring system evaluations four hours apart should receive immediate treatment for withdrawal symptoms. Those newborns displaying a high objective measurement of GI disturbances are recommended to have a toxicology screening of bowel movements as well as a urinalysis.[5]

Complications
Complications of NAS include birth defects, premature birth, low birth weight, small head circumference, failure to thrive and sudden infant death syndrome (SIDS). Due to the wide variety in prenatal exposure to the drug, duration, and total exposure dose, long-term effects are not well characterized. Withdrawal symptoms can be controlled and resolved, but

damage resulting in birth defects will likely lead to a permanent decrease in quality of life for the child.[1,6] Specific long-term effects on quality of life include poor school performance and learning disabilities.[3] While NAS can cause long-term reduced quality of life, most neonates born with NAS can experience complete symptom resolution with pharmacological agents and will not experience long-term complications.[6]

Treatment Considerations

There are many different treatment options for NAS, and treatment selection is based upon what drug the newborn was exposed to and, as a result, the presentation of symptoms. NAS can be caused by either opioid exposure or non-opioid exposure as mentioned previously. Symptoms caused by opioid exposure fall into three main categories: neurological, gastrointestinal and autonomic.[1,2] According to a study done by Rosen and Pippenger, the most common symptoms that occur in neonates with NAS are tremor, hypertonicity and irritability, all occurring at rates of 86 percent.[7] The least common symptoms cited were diarrhea (14%) and fever (17%).[7] Specific treatment options that target each grouping of symptoms often overlap and a mixture of all three types of symptoms are seen.[8]

The first type of treatment that all NAS newborns receive (both opioid exposed and non-opioid exposed infants) is nonpharmacologic, which is the preferred intervention when possible.[9] Nonpharmacologic treatment is centered on calming the newborn, and consists of methods such as swaddling, rocking, providing minimal sensory or environmental stimulation, maintaining the newborn's temperature, maintaining a consistent feeding schedule and using breast milk if possible.[9] One caution with breast-feeding includes the fact that

drugs can be passed to the newborn through breast milk. Therefore, if the mother is still using illicit or prescription drugs that are excreted in breast milk, the risks of further drug dependence outweigh the benefits of breast-feeding.[10] Additionally, due to the potential dehydration, vomiting and diarrhea that may occur with NAS, another important aspect of nonpharmacologic therapy is to maintain intravenous (IV) hydration in the neonate.[9]

Pharmacologic treatment is initiated based upon scores from the Finnegan NAS scoring system as mentioned previously. Pharmacologic treatments generally fall into two separate categories: opioids and non-opioids.[9] Opioids are the main cause of NAS; as a result, this is the area of focus for pharmacologic treatment. For opioid-exposed newborns with NAS, treatment options include opium tincture, morphine, methadone and buprenorphine (see Table 1 for administration directions).[9] While all these options are opioids themselves, they are used to wean the infant off opioids slowly while trying to minimize withdrawal symptoms. Previously, opium tincture was the agent of choice, but it has fallen out of favor as morphine has gained prominence. Currently, morphine is the most commonly used opioid treatment option given to the symptomatic newborn after birth.[9]

An alternative to morphine is methadone. Methadone is also the recommended agent by the U.S. Department of Health and Human Services to give to the mother during pregnancy to help both the mother and child. Their guidelines state that methadone maintenance should be the first-line option for opioid-dependent women during pregnancy, and that morphine should be given to opioid addicted women during pregnancy only if methadone is not available. These guidelines also state that opioid detoxification should not be ad-

Table 1. Benefits and Limitations of NAS Treatment Options.[12,13]

Medication	Benefits	Limitations
Morphine	Most studied Proven efficacy	Frequent dosing Long withdrawal period
Methadone	Less frequent dosing Approved for use in pregnancy Appear to be the safest	Difficult to wean State and federal regulations
Buprenorphine	Less frequent dosing Less respiratory depression (compared to morphine and methadone) Less abuse potential	Ceiling effect Higher failure rates (compared to morphine and methadone) Least studied
Opium tincture	Well studied Proven efficacy	Contains alcohol and alkaloids Frequent dosing

ministered to every pregnant woman due to the high risk of relapse seen when opioids are the initial drug of abuse.[10] Buprenorphine in NAS treatment is currently being researched. It is primarily used in adults to treat withdrawal symptoms, but also has potential in neonates. In a study done by Fischer and colleagues, mothers were maintained with buprenorphine during pregnancy, although neonates were treated with morphine after birth. Out of the 15 opioid-dependent pregnant women included in the study, NAS was absent in eight of the neonates, mild in four neonates, and moderate in three neonates.[10] Buprenorphine was well tolerated by both mother and fetus during pregnancy, but because there have been no large trials done with buprenorphine in neonates, it is still not recommended as a first-line treatment for NAS.[11] Figure 1 provides an example treatment algorithm of the type that may commonly be developed at an institutional

Figure 1. Example Treatment Algorithm for NAS
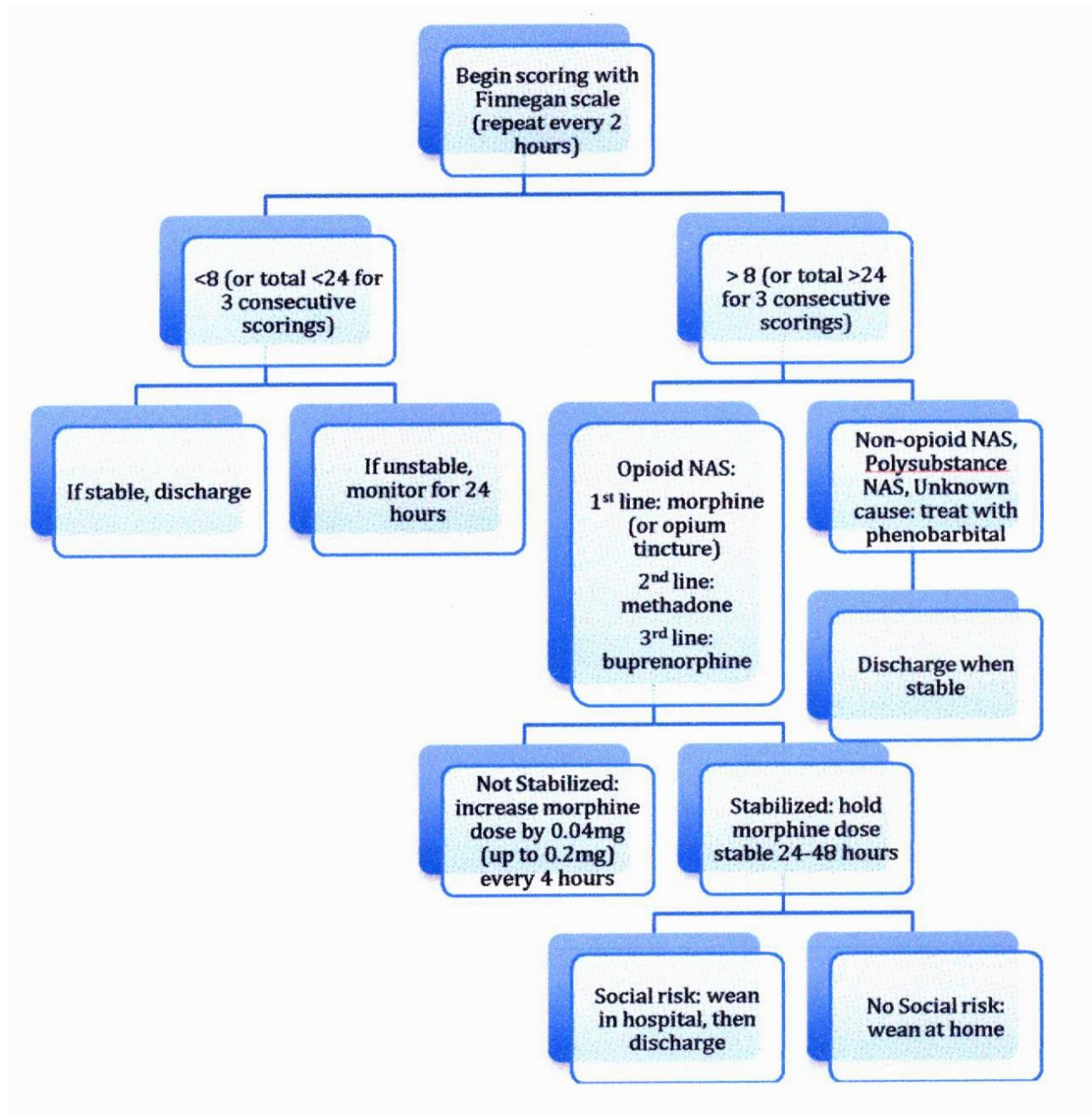
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Table 2. Common Dose, Administration, and Taper Duration for NAS Treatment Options.[4,14,15]

Medication	Dose	Route of administration	Taper duration
Morphine	0.04mg/kg/dose (max 0.2mg/kg/dose) for 2-3 days	Oral	2 to 7 days
Methadone	0.5mg/kg/day in divided doses q8h	Oral, IV	1 to 1.5 months
Buprenorphine (limited data)	5.3mcg/kg/dose q8h for 3 days	Sublingual	unspecified
Opium tincture	0.04mg/kg/dose q3-4hr for 3-5 days	Oral	2 to 4 weeks

level to treat NAS.[A,B]

The second category of pharmacologic treatment includes non-opioid treatments that are intended to provide symptomatic relief.[12] Non-opioid treatments for symptomatic relief of NAS have traditionally included two sedatives (phenobarbital or diazepam), an antiemetic (chlorpromazine) and an antihypertensive (clonidine). Phenobarbital is used to treat the hyperactive behavior that may accompany opioid withdrawal and is used preferentially over diazepam.[12] Clonidine is used to inhibit sympathetic nervous system output; therefore, it decreases the autonomic side effects seen in opioid withdrawal such as tachycardia, hypertension, restlessness, and diarrhea.[16] Chlorpromazine has been used in the past as an antiemetic if necessary; however, it has limited usefulness due to adverse reactions such as hypothermia and a decrease in the seizure threshold. It is important to avoid this decrease in seizure threshold because seizures are a common manifestation of opioid withdrawal.[17] Non-opioid treatment options should be considered for relief only if opioid withdrawal effects become too severe.

Ultimately, there are several challenges that pharmacists face when evaluating treatment options for NAS. One challenge is the lack of randomized controlled trials regarding optimal detoxification in neonates. Given that immediate treatment is required in neonates, as long as there are therapies and drug options that work, few trials will be conducted to discover if other alternatives would be superior. Another challenge in treating NAS is maternal adherence to treatment. In cases of accidental and illicit drug consumption during pregnancy, a change in maternal drug usage will most likely be seen if it is discovered that the newborn has NAS. These mothers are typically more adherent to infant treatment if the newborn has NAS. However in cases of illicit drug use where the mother does not adhere to any sort of treatment during pregnancy, the neonate may face difficulties once discharged from the hospital.[10]

Role of the Pharmacist

Neonatal abstinence syndrome is a complex disease state that impairs the quality of life of an extremely vulnerable patient population. Ultimately, the management of this disease state should be overseen by a team of health care professionals, including a pharmacist, who work together dynamically to achieve optimal patient outcomes. As a medication and pharmacology expert, the pharmacist is in a unique position to positively impact NAS patient outcomes. More specifically, the pharmacist can make recommendations regarding drug therapy choices, play a critical role in the education of both the health care providers and the affected families, aid in the development of system-wide protocol for the treatment of NAS and help to inform the public on the implications of substance abuse during pregnancy. This wide array of interventions allows the pharmacist to substantially impact patient care in both the community and inpatient setting.

The community pharmacist is in an ideal position with regard to the education of the public. Pharmacists are dispensing more opioid products now than in the past. According to the National Institute on Drug Abuse, 210 million opioid prescriptions were dispensed by community pharmacies in 2010, up from 131 million in the year 2000.[18] Along with this fact, legal substances (such as opioids) have replaced illicit substances (such as heroin or cocaine) as the most common cause of fatal drug poisoning in the United States.[19] In fact, data suggest that in 2005, oxycodone usurped all illicit drugs in the category of nonmedical abuse; the most blatant reason for this shift being ease of access.[20] One major study suggests that the rate of maternal opioid abuse increased fivefold between 2000, and 2009, while the rate of NAS diagnosis has increased threefold in the same timeframe.[21]

In an effort to prevent the circumstances that precipitate NAS, the community pharmacist should remain vigilant in the fight against opioid abuse. Pharmacists should be on the

alert for patients who consistently claim lost prescriptions, emergency department prescriptions, display opioid-seeking behavior and those who refuse and are unwilling to alter their treatment.[20] Many states have developed integrated databases that allow for tracking an individual's history with drugs that possess a high abuse potential.[22] In particular, if these behaviors are witnessed in a pregnant female, the pharmacist should take it upon himself/herself to provide a robust education to the patient about the potential implications of this behavior on the unborn child.[20] One way to ensure that counseling reaches the patient in a time-appropriate manner is to target education and counseling to individuals coming to the pharmacy to purchase prenatal vitamins.

One critical population to monitor is pregnant women with mental health issues. One study showed that over the span of one year, 45 percent of children born with NAS were born to a female parent with psychiatric illness.[23] Studies show that use of antidepressants while pregnant have not been found to damage development of the fetus, whereas noncompliance with antidepressants are linked to increased substance abuse and therefore development of NAS in the child. As pharmacists, the opportunity exists to educate patients about medication adherence and to ensure patients are taking their medications properly.[24]

In addition to prevention of the disease state in the community, the pharmacist should be involved at an institution level to develop a protocol for the treatment of NAS. Due to the diverse symptomatology associated with NAS, in addition to the lack of high quality evidence regarding treatment, it is important to establish a thorough protocol.[13] This protocol should then be referenced by physicians and pharmacists alike throughout the treatment process in order to ensure consistent treatment for each patient. By utilizing a standard protocol throughout the system, it becomes much easier to identify specific ways to improve overall levels of care to achieve improved outcomes over time. Unfortunately, this system-by-system approach to NAS protocols makes it even more difficult to come to an overall consensus on how to optimally treat the disease state.

Furthermore, once treating individual patients for NAS, the pharmacist should make it a priority to offer counseling services to the affected families.[25] Always be sure to put aside personal opinion and approach the situation as a professional. Mothers, in particular, are in critical need of education and must be informed of proper treatment and care techniques. Additionally, NAS prevention education should still be given in order to protect against NAS in future pregnancies and any issues that could present themselves during breast-feeding.[25] Due to this fact, family counseling should be a priority for pharmacists not just in the treatment of NAS but for all major pediatric conditions.

Finally, the pharmacist should be a strong resource for the health care team regarding proper pharmacologic management of NAS. As previously noted, the treatment for NAS can often be quite complex and is heavily dependent on several factors that differ in individual pregnancies. Given the current lack of high quality evidence regarding the treatment of NAS, it is critical that the pharmacist continue to be cognizant of advances in the field of neonatology and be willing and able to discuss new findings with all members of the health care team, particularly the primary prescribers. Ultimately, the pharmacist should be a critical force in providing information for the health care team as a whole.

Conclusion

NAS describes an array of issues that present in newborns soon after birth. Ultimately, symptomatology will vary widely based upon the specific substance utilized by the mother while pregnant and duration of exposure. Clinically, treatment is essentially divided based upon an opioid-derived abstinence syndrome versus a non-opioid derived abstinence syndrome. Treatment is focused on providing supplemental pharmacologic agonist effects for the source of the withdrawal. Due to the intricate nature of treating NAS, management of the disease state should be overseen by a team of health care professionals, including a pharmacist. Both clinical pharmacists in the inpatient setting and community pharmacists in the outpatient setting are in uniquely strategic locations to prevent and/or positively impact the outcomes for NAS.

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Assessment Questions

1. After birth, most newborn babies will show signs of withdrawal within
   A. 2 to 4 hours
   B. 12 to 24 hours
   C. 24 to 48 hours

2. Neonatal abstinence syndrome (NAS) is most closely related to maternal use of:
   A. Alcohol
   B. Illicit substances
   C. Prescription medications
   D. Both a and b
   E. Both b and c

3. Initial screening of NAS includes use of:
   A. Finnegan scoring system
   B. Urinalysis
   C. GI toxicology screening

4. Complications of NAS include all of the following except:
   A. Failure to thrive
   B. High birth weight
   C. Small head circumference
   D. Sudden infant death syndrome (SIDS)

5. True or False? Neonates with NAS only show symptoms from one of the three categories of symptoms: neurological, gastrointestinal, or autonomic.
   A. True
   B. False

6. Nonpharmacologic treatment options include
   A. Swaddling
   B. Maintaining a consistent temperature
   C. Giving a consistent feeding schedule
   D. All of the above

7. What is the correct first-line treatment and dose for newborns with NAS?
   A. Morphine 0.04 mg/kg/dose
   B. Morphine 0.4 mg/kg/dose
   C. Buprenorphine 5.3 mcg/kg/dose
   D. Opium tincture 0.4 mg/kg/dose

8. Which of the following is a benefit of buprenorphine for treating newborns with NAS?
   A. It is well-studied
   B. It is the drug of choice in pregnant women
   C. It has a ceiling effect
   D. It has a low abuse potential

9. Which of the following describes a major role that community pharmacists can have regarding NAS?
   A. Refusing to dispense addictive medications to pregnant women
   B. Targeting education to women purchasing prenatal vitamins
   C. Helping to promote control of mental disorders through medication compliance
   D. Two of the above
   E. All of the above

10. Which of the following describes a major role that inpatient pharmacists can have regarding NAS?
    A. Focus only on the patient when providing counseling
    B. Help to develop an institution-specific protocol for treating NAS
    C. Avoid pain control medications in pregnant women
    D. Two of the above
    E. All of the above

To receive continuing education credit for this program, you must answer the above questions and fill out the evaluation form. Please visit www.onu.edu/pharmacy to enter the required information. Please allow two to three weeks for electronic distribution of your continuing education certificate, which will be sent to your valid email address in PDF format.

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Pharmacy License #:	**State:**	**ONU Alumni?**	**Y**	**N**

Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals and objectives:					
Explain the etiology, patient presentation and diagnosis of neonatal abstinence syndrome (NAS).	1	2	3	4	5
Describe perceived complications of NAS.	1	2	3	4	5
Describe nonpharmacologic treatment options for treating NAS.	1	2	3	4	5
List pharmacologic treatment options for opioid exposed NAS, as well as benefits and limitations for each medication.	1	2	3	4	5
Identify several ways that a pharmacist can impact the care of a patient with NAS.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

_____

_____

_____

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C
2. A B C D E
3. A B C

4. A B C D
5. A B
6. A B C D

7. A B C D
8. A B C D
9. A B C D E

10. A B C D E

Achieving Provider Status for Pharmacists

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Abstract

In order to receive payment for medical services through Medicare Part B, health care professionals must be identified as "providers" under the Social Security Act. Pharmacists currently are not included in the list of providers and, therefore, cannot provide many services to patients. Through their extensive education and training, accessibility and immense trust in their profession, pharmacists are the ideal health care professionals to help expand the continuity of care of our nation's patients. On Jan. 1, 2014, Senate Bill 493 was passed into law recognizing pharmacists in the state of California as providers. With this new legislation, the pharmacists' role in health care, as well as the patient's access to care, will be greatly expanded nationally. It is important for pharmacists and students to advocate at the state and federal level to expand provider status to all states in order to advance the profession of pharmacy.

Introduction

Pharmacists and pharmacy-based services are currently not included in section 1861 of the Social Security Act (SSA) which regulates compensation eligibility for health care programs such as Medicare Part B.[1] Medicare recognizes certain health care professionals as "providers" in section 1861, and authorizes them to bill and receive payment from Medicare Part B for services that fall within their state's scope of practice. Those listed as providers include physicians, physician's assistants, certified nurse practitioners, qualified psychologists, clinical social workers, certified nurse midwives, certified registered nurse anesthetists, qualified speech language pathologists, qualified audiologists, registered dietitians and physical therapists.[1,2]

The exclusion of pharmacists as providers under the SSA severely hinders the ability of pharmacists to provide a variety of services of which they are capable.[2] Failure to recognize pharmacists as health care providers prevents coverage of pharmacy services in the outpatient setting under Medicare Part B and prohibits pharmacists from receiving reimbursement for comprehensive patient services when they are provided. Exclusion from the provider list can also prevent the inclusion of pharmacists in interdisciplinary care delivery models associated with the Affordable Care Act (ACA), such as patient-centered medical homes (PCMHs) and accountable care organizations (ACOs).

Achieving better patient outcomes in a cost-effective manner is a major goal of health care reform.[2] A major component of meeting this goal is ensuring the proper education, administration and use of medications. Each year more than 1.5 million preventable medication-related adverse events occur within the United States, resulting in nearly $290 billion in avoidable health care system costs.[3,4] Medication non-adherence alone is responsible for nearly $100 billion each year in excess hospitalizations.[5] Pharmacists have advanced knowledge and training in proper medication use and can provide services to patients focused on the treatment, management and prevention of diseases, including Medication Therapy Management (MTM), medication reconciliation, ambulatory care monitoring, disease state management, smoking cessation, immunizations and, most importantly, patient education.[2] The rising number of individuals newly insured under the ACA, increasing age of a large portion of the population and shortage of primary care providers presents a pressing need for improved health care medication management. Pharmacists have the opportunity to fulfill this need by engaging patients in a more proactive approach to health care and improving the quality of outcomes for more people.

Benefits of Pharmacists' Involvement in the Health Care Team

Pharmacists have shown to provide many benefits to the health care system by providing their expertise in medication and disease management, treatment and prevention.[2] Their accessibility to a wide variety of patients, the foundation of trust in the profession and their extensive knowledge in complex drug regimens and nonpharmacologic treatment allows pharmacists to have a dynamic impact on the health care of our nation. Pharmacists are known as the medication experts among the health care professions, and medications are shown to be involved in 80 percent of treatments. However, pharmacists are still not recognized as health care providers. Pharmacists complete an intense curriculum including classes in therapeutics, pharmacology, clinical skills, problem solving, pharmacokinetics, laboratory monitoring and pathophysiology.[6] They are required to participate in patient-centered clinical experiences and are required to have a similar level of education as most nonphysician health care professionals. As part of their training, pharmacists are prepared to deliver health care via primary prevention, comprehensive medication reviews, disease state management and patient counseling. The vast education and training of a pharmacist allows them to provide immense benefit to the health care team, and this benefit can only be fully utilized by granting pharmacists provider status.

Pharmacists have been known for years as one of the most trusted professions, and the accessibility of pharmacists makes them a potential asset in aiding physicians in improving continuity of care and patient outcomes.[6] With fewer numbers of primary care physicians, the accessibility of pharmacists can help close the gap of those who are not being treated to help meet the demand of the health care system. Most pharmacies are open seven days a week, and some are open 24 hours a day. According to the report to the Surgeon General in 2011, 270 million people visit a pharmacy

each week. There is a community pharmacy located within five minutes of most Americans, making pharmacists accessible even in areas of scarce medical resources.[7] By granting pharmacists provider status, these visits may help lessen the overwhelming burden on physicians, provide better care for patients and present the ability for pharmacists to use their experiences and background to improve the health care system.[6]

With the immense training that pharmacists complete, they are extremely proficient in managing chronic disease states such as asthma, hypertension and diabetes.[7] By allowing pharmacists to become providers and help further manage patients' medications and chronic diseases, health care costs can be reduced. They are able to help avoid adverse events by providing clinical interventions when warranted.[6] In 2009, the U.S. health care system spent $1.7 trillion on chronic diseases, which equates to be about 75 cents spent on chronic diseases per $1 spent on health care. The cost-effectiveness of pharmacists' intervention is evidenced by projects and studies such as the Asheville Project.[8] The Asheville Project was started by the city of Asheville, N.C., as an effort to reduce the health care costs of its employees. The project established a community-based, pharmacist-driven program to manage the chronic disease states of its employees such as diabetes, asthma, hyperlipidemia and hypertension. The management of these patients' disease states (particularly the patients with asthma) by pharmacists yielded a cost savings of nearly $1,955 in direct and indirect costs per year. Pharmacists are able to select appropriate medication use for each patient, monitor patient outcomes and, in turn, reduce the overall health care costs especially those associated with chronic diseases.[6]

Initiating Movement
There has already been a shift in health care in which pharmacists are working with physicians to directly impact patient care by collaborating together to manage a patient's disease states, medication use and adherence.[2] As previously mentioned, pharmacists are extensively trained to be able to help relieve some of the overwhelming burden physicians are now facing. With the deficit in physicians rising to almost 50,000, pharmacists can provide a new approach to delivering health care to patients. Collaborative practice agreements are already in place in which pharmacists, physicians and other health care professionals are involved in multiple aspects of the patient's care creating a seamless approach and improvement of the health care continuum.[9] For many years, the pharmacists in the Public Health Service (PHS), Indian Health Service (IHS), and Veterans Affairs (VA) have been practicing as providers in the government sector.[6,10] They use complete health records to counsel patients on their disease states and medications and are able to directly dispense medications based on certain protocols. The use of pharmacists in these settings have shown a return on investment (ROI) of 4:1, meaning for every one dollar invested with the use of pharmacists, a four dollar savings in health care spending occurs.[10] With pharmacists already taking on this role, it is evident that pharmacists as health care providers will increase the ability for the health care system to meet

the needs of patients and will continue to build interprofessional relationships.[9]

The American Pharmacists Association (APhA) has led the initiative pushing forward the profession of pharmacy, hoping to be recognized for the pharmacist's role in collaborative patient care.[2] The APhA has been using their political action committee to push at the national level for this recognition. Their board of trustees has allocated $1.5 million to allow for a long-term goal of achieving provider status. The APhA is also a part of the Patient Access to Pharmacists' Care Coalition (PAPCC) along with 22 other national organizations and companies including American Society of Consultant Pharmacists (ASCP), American Society of Health-System Pharmacists (ASHP) and the National Community Pharmacists Association (NCPA). The PAPCC is leading the legislative ask to allow pharmacists to practice as providers.[11] The goal of the PAPCC is to obtain provider status under Medicare Part B for pharmacists within their scope of practice in medically underserved areas. They are trying to accomplish this by bringing awareness to Congress at the federal level. On March 11, 2014, the PAPCC introduced a bill to the U.S. House of Representatives (H.R. 4190) which is intended to amend title XVIII of the SSA to allow for coverage of patient care services provided by pharmacists.[12] This is important to the profession of pharmacy because it allows pharmacists to not only improve the quality of patient care, but also to continue to be relevant health care practitioners in the ever-changing U.S. health care system.

California and Pharmacist Provider Status
California is the first state to draft a proposal for health provider status for pharmacists, and have it signed into law.[13,14] Introduced on Feb. 21, 2013, Senate Bill (S.B.) 493 "declares pharmacists as health care providers who have the authority to provide health care services." After gaining momentum from the approval of various pharmacy organizations, it was officially signed on Oct. 1, 2013, by Gov. Jerry Brown and went into effect Jan. 1, 2014.[15] With millions of newly insured patients and the number of primary care physicians continually growing smaller, this law is a crucial step in the right direction toward improving patients' access to care by pharmacists. Not only will the law expand the roles of pharmacists in California, but it will also pave the way for similar legislation in other states.

On Jan. 1, 2014, there were a number of provisions of S.B. 493 that went into effect that significantly enhanced pharmacists' role in patient care.[14] The new law allows all licensed pharmacists to administer oral, topical and injectable drugs and biologics (vaccines, blood and blood components, gene therapy, etc.) as ordered by prescribers.[16] Previously, administration was limited to oral and topical medications, and injectable medications were excluded.[14]

Pharmacists in California can now provide consultation, training, education of drug therapy and management and prevention of various disease states.[14,17] In addition, pharmacists are now allowed access to patient medical records to improve medication management and to better participate in

the review and monitoring of patient progress. The provision that authorizes pharmacists to order and interpret tests to determine efficacy and toxicity of drug therapy in coordination with the patient's primary care provider will also improve the patient's medication management overall.

The law grants pharmacists the ability to furnish or supply Centers for Disease Control recommended travel medications that do not require a diagnosis.[14,17] It also permits pharmacists to administer immunizations to patients 3 years of age and older as long as the required training, certifications and recordkeeping requirements are met. If a pharmacist wants to immunize a child younger than 3 years of age, a physician protocol is needed. This reduction in age expands the number of patients allowed to receive immunizations from local pharmacists, which will increase total access to immunizations and improve overall public health.

Many of the provisions included in S.B. 493 need further regulations that will not be finalized until the end of 2014, or later.[14,17] By the end of this year, pharmacists in California ought to be able to furnish self-administered hormonal contraceptives and prescription nicotine replacement products in accordance with a statewide protocol after proper certification and training. With the addition of these provisions, the barriers patients face when trying to gain access to contraceptives will hopefully be reduced, and there will be wider access to smoking cessation products.

Provisions, that will most likely not be finalized until after 2014, are to establish an Advanced Practice Pharmacist (APP).[14,17] Pharmacists seeking APP recognition must complete two of the following:

- Earn certification from an organization recognized by the board in a relevant area of practice (pediatric, geriatric, ambulatory care, pharmacotherapy, etc.)
- Complete a one-year postgraduate residency where 50 percent of the experience includes direct patient care services with interdisciplinary teams
- Actively manage patients for at least one year under a collaborative practice agreement or protocol with a physician, APP, pharmacist practicing collaborative drug therapy management or health system.

In addition to current continuing education (CE) requirements, a pharmacist must hold an active pharmacy license and complete 10 hours of CE in at least one area relevant to a pharmacist's clinical practice in each renewal cycle. Recognition of APP will be valid for two years.

An APP is authorized to perform patient physical assessments, order and interpret drug therapy-related tests and refer patients to other health care providers.[17] Advanced Practice Pharmacists can also initiate, adjust and discontinue medication therapy in accordance with the protocol provided by the patient's prescriber. With the role of pharmacists' moving beyond just dispensing medication, their active involvement in team-based care can improve chronic disease management. Advanced Practice Pharmacist recognition permits pharmacists to participate in the evaluation and man-

agement of diseases and conditions within these health care provider teams. The progress made by S.B. 493 lays the foundation for the advancement of the pharmacy profession, and provides an example for other states to follow suit with their own legislation.

How Students and Pharmacists Can Get Involved
It is more important now than ever for pharmacists and students to become involved in advocating for the profession of pharmacy.[2] Most legislators do not know what pharmacists actually do besides dispense medications, but they appreciate hearing from the people they serve. By educating them, we can become closer to the goal of provider status. Schedule an appointment with your legislators. Tell them about what pharmacists do and the role they already play in patient care. If going to the state house to educate your state representatives sounds too intimidating, invite them to come observe you for a day in your practice as a pharmacist or pharmacy intern. This can be beneficial because they can actually see what happens day-to-day in the life of a pharmacist and may lead to a new respect for pharmacists. Another way to help is to find physicians, physician's assistants, and other health care practitioners, as well as patients, who see the value pharmacists bring to health care and understand the benefit they could provide as health care providers. Ask these people if they would be willing to contact their representative on the profession of pharmacy's behalf. The APhA has many opportunities to sign up to volunteer at various events advocating the profession of pharmacy. These opportunities can be found on their website (www.pharmacist.com). Pharmacists and students can join national pharmacy organizations and attend professional meetings in order to learn more about how to help. Pharmacists and pharmacy students need to become part of the team pushing for the same goal of achieving provider status. By advocating the profession at every opportunity, the pharmacy community can achieve this goal together.

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Answers About the Need for Vitamin D Supplementation

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Abstract
Vitamin D has a significant role in bone health, calcium homeostasis, immune function and other biological functions. In our bodies, the main source of vitamin D is linked to our skin's exposure to sunlight. It can also be obtained through foods that contain vitamin D. Despite these two sources, vitamin D supplementation is often necessary. It is available in two forms, cholecalciferol and ergocalciferol as over-the-counter (OTC) products, as well as calcitriol as prescription only. Reasons for vitamin D deficiency include lack of sunlight, poor diet, malabsorption of vitamin D, liver and/or kidney disease. Vitamin D deficiencies lead to diseases such as rickets, osteomalacia and osteoporosis. During supplementation it is important to monitor for vitamin D toxicity. Pharmacists need to be aware of the various guidelines regarding vitamin D supplementation.

Introduction
Vitamin D, a fat-soluble vitamin, is important for overall health and well being in both adults and children. In recent years, vitamin D deficiency has been "over-hyped," and claims that supplementation can 'cure' various disease states have been unsubstantiated. Recommended daily doses also continue to vary between different governing bodies, including the National Osteoporosis Foundation (NOF) and the Institute of Medicine (IOM). Additional inconsistency exists in the literature concerning normal plasma vitamin D levels which then defines vitamin D deficiency. Due to vitamin D's significant role in bone health, calcium homeostasis, immune function, and other biological functions, many foods in the United States are fortified with vitamin D.[1]

How We Get Vitamin D
The main source of vitamin D in our bodies is derived from our skin secondary to sunlight exposure. Skin uses ultraviolet (UV)-B rays (290 nm - 315 nm) to convert 7-dehydrocholesterol to cholecalciferol, which is also referred to as vitamin D_3. Cholecalciferol is transported to the liver via a vitamin D binding protein where it is converted by the enzyme 25-hydroxylase to calcifidiol which is also referred to as 25-hydroxycholecalciferol abbreviated 25(OH)D, calcifidiol or *calcidiol*.[2] Calcifidiol is then transported to the kidney where it is converted to calcitriol by the enzyme 1-alpha hydroxylase. Calcitriol, which is also referred to as 1,25-dihydroxycholecalciferol (abbreviated 1,25(OH)2D), is the most biologically active form of vitamin D. It is utilized to carry out various physiological functions, namely aiding our body in the absorption of calcium.[2] As previously stated, vitamin D is synthesized by the body in response to sunlight exposure, therefore any increased pigmentation will act as a natural sunscreen and ultimately reduce the amount of vitamin D that is produced from UV-B exposure. Vitamin D can also be obtained naturally from food sources such as oily fish like cod, mackerel, salmon and sardines while milk, cereal, yogurt and orange juice are fortified with vitamin D.[3]

Vitamin D Products
Although vitamin D is found in many foods and is readily activated in the skin by the sun, supplementation may be necessary to maintain an overall healthy state. Over-the-counter (OTC) sources of vitamin D contain either the compound cholecalciferol or ergocalciferol, which are commonly referred to as vitamin D_3 and vitamin D_2 respectively.[4] Ergocalciferol (vitamin D_2) is a plant-derived source, while supplemental cholecalciferol (vitamin D_3) is a synthetic form similar to what the body synthesizes in the skin via UV exposure.[5] It is important to note that cholecalciferol and ergocalciferol have both OTC and prescription products as outlined in Table 1.[4] Calcitriol, the active form of vitamin D, is only available by prescription.[5] Calcitriol is reserved for individuals with idiopathic and postsurgical hypoparathyroidism, pseudohypoparathyroidism and secondary hyperparathyroidism in those with moderate to severe chronic renal failure not yet on dialysis, and also those undergoing chronic renal dialysis. These individuals cannot convert calcifidiol to calcitriol in adequate amounts to maintain physiologic levels of plasma calcium. More information on specific dosage forms and doses are outlined in Table 1.

Vitamin D Deficiency
Common causes of vitamin D deficiency include lack of exposure to sunlight, poor diet and/or malabsorption of vitamin D. Medications such as phenobarbital, phenytoin, orlistat and corticosteroids can also lead to vitamin D deficiency. Phenobarbital decreases hepatic metabolism of vitamin D, specifically impacting the cytochromes responsible for the activity of vitamin D-25 hydroxylases that convert cholecalciferol to calcifidiol.[6] Phenytoin also induces activity of the cytochrome P450s in the liver and may additionally affect bone formation and resorption, calcium absorption and response of osteoblasts to parathyroid hormone.[7] Orlistat, brand name Alli®, was found to decrease the levels of 25-OH vitamin D even with the subjects taking multivitamins containing 400 IU of ergocalciferol.[8] Orlistat works by decreasing absorption of dietary fats, thus absorption of vitamin D, a fat-soluble vitamin, would also be expected to be negatively impacted.[9] Malabsorption conditions such as inflammatory bowel disease (IBD), cystic fibrosis (CF) and celiac disease may affect vitamin D absorption as well.

Additional causes of vitamin D deficiency include both liver and chronic kidney disease, as both organs are needed to convert vitamin D to its active metabolite. Plasma levels of calcifidiol (25-hydroxycholecalciferol or (25-OH)D) are measured to determine nutritional deficiency of vitamin D and/or lack of sunlight exposure. Plasma levels of calcitriol

Table 1. Vitamin D Products Including Dosage Form and Dose.[4]

		Capsule	Tablet	Liquid	Other
OTC Products	**Cholecalciferol**				
	Vitamin D_3 Super Strength	1,000-50,000 units	400-5,000 units & 50,000 units	400 units/mL & 2,000 units/0.3 mL & 5,000 units/mL	
	Ergocalciferol				
	Vitamin D_2		400 units & 2,000	8,000units/mL	
Rx Products	**Cholecalciferol**				
	Vitamin D_3 Super Strength	25,000 units (Decara)			
	Ergocalciferol				
	Vitamin D_2	50,000 units			
	Calcitriol				
		0.25 mcg & 0.5 mcg		1 mcg/g	Ointment 3 mcg/g
					IV Solution 1 mcg/g

(1,25-dihydroxycholecalciferol or 1,25(OH)2D are used clinically to confirm diagnosis of vitamin D deficiency rickets, parathyroid disorders and deficiencies in renal function.[10] Plasma vitamin D levels are not used diagnostically or to define a nutritional deficiency because this level will only provide data on recent sunlight exposure.[11]

Disease of Vitamin D Deficiency
Vitamin D deficiencies contribute to the development of diseases such as rickets, osteomalacia and osteoporosis. These conditions are characterized by weak bones, deficient vitamin D levels and, possibly, consequential hypocalcemia. All three impair the process of bone mineralization which relies on vitamin D to increase plasma calcium levels via increased intestinal absorption and decreased renal excretion. However, they differ in regard to the locations that are impacted. Osteomalacia occurs in regular bone, whereas rickets occurs specifically at growth plates and thus is a disease that can only affect growing children. Osteomalacia is often challenging to diagnose, but can be identified by bone pain, specifically in axial bones such as the legs and a 'waddling' gait.[12] Treatment of osteomalacia is very basic, focusing on relieving the pain and preventing fractures. Treatment consists of supplementation with vitamin D, calcium and possibly phosphate. When possible, the cause should be determined and rectified.[12]

As mentioned, rickets is characterized by issues at growth plates, which sets it apart from osteomalacia. Depending on the age of the pediatric patient, the manifestation of rickets can vary.[12] Neonatal growth occurs most rapidly in the skull, so rickets will manifest in skull formation in that subpopulation. In children 1 year of age, rickets will manifest in the wrists and rib cage, while inward or outward bowing of the legs is seen in toddlers.[12] The type of rickets (primary versus secondary) is defined by the cause of vitamin D deficiency. Primary or nutritional vitamin D deficiency is caused by either inadequate diet or inadequate exposure to sunlight.[12] This diagnosis is confirmed with testing for 25-OH vitamin D levels in the blood. If the level is low, treatment with calciferol is initiated.[12] Secondary vitamin D deficiency is caused by another disease state (such as gastrointestinal disease, pancreatic diseases, hepatic diseases, celiac disease or primary biliary cirrhosis) that impacts absorption of vitamin D.[12] Treatment is the same as primary vitamin D deficiency: calciferol supplementation. Calcium deficiency, also known as calciopenic rickets, can exacerbate vitamin D deficiency rickets. Adding calcium, either through diet or supplementation, will correct calciopenic rickets. Metabolic acidosis can also cause rickets, but this condition is easily treated with vitamin D supplementation and alkali therapy.[12] Certain genes can also contribute to rickets. X-linked hypophosphatemia (XLH) is a hereditary condition in which the patient's ability to convert vitamin D to its active form is

changed. The XLH patients will present with a short stature and bowed limbs but not the fractures or muscle weakness associated with other forms of rickets.[12] Standard treatment is calcitriol, the activated form of vitamin D, and phosphate tablets.[12] With XLH, activated vitamin D is given because the patient is not able to convert the inactive forms into the usable active forms. Other genetic defects can cause issues in either the synthesis of vitamin D or produce resistance in the tissues to vitamin D.[12]

Osteoporosis is another disease related to vitamin D deficiency. With osteoporosis, bone is either not being formed, mineralized or is breaking down.[13] A patient with osteoporosis has a loss of bone density, which predisposes them to fractures. Physical symptoms of osteoporosis include loss of height over time or a stooped back due to weak vertebrae that can collapse or break easily.[14] Osteoporosis affects 52 million Americans and costs approximately $19 billion a year.[14] Osteoporosis is linked with deficiencies in calcium, hormones such as estrogen and vitamin D.[15] Vitamin D has a role in the pathophysiology of osteoporosis due to its involvement in calcium homeostasis. Calcium is a necessary mineral required for bone formation and maintenance, and it cannot be absorbed from the gastrointestinal tract without vitamin D.[15,16] Specifically, vitamin D stimulates the synthesis of calbindin, a transport protein for calcium. This protein moves calcium from the apical side of mucosal cells of the gastrointestinal tract (GIT) to the basolateral side, which is in contact with systemic circulation.[16] Because of its role in the absorption of calcium, supplementation of both vitamin D and calcium is recommended for osteoporosis patients.[17] In the Decalyos II study, investigators found that, compared to placebo, both those taking a combination tablet (1200 mg calcium and 800 IU vitamin D) and the two ingredients simultaneously in two separate tablets experienced significantly improved vitamin D levels and lower parathyroid hormone (PTH) levels when compared to placebo.[18] Parathyroid hormone is released when plasma calcium levels are low. Parathyroid hormone stimulates vitamin D activation and calcium resorption from the bone, and a lowering of PTH is indicative of increasing calcium levels.[19] The 389 subjects taking both vitamin D and calcium had an unchanged bone density test after 12 months while the placebo group (n=194) saw a decrease in bone density in both the femur and the radius, but the change was not found to be statistically significant (p=0.09, p=0.48 respectively). This double-blinded study supports supplementing with both vitamin D and calcium in patients diagnosed with osteoporosis to prevent disease progression.[18]

Influence of Malabsorption Disorders on Vitamin D
Kuwabra et al., using a value of less than 15.7 ng/ml as their definition of vitamin D deficiency, investigated the incidence of vitamin D deficiency in those with IBD, Crohn's disease and ulcerative colitis. They reported that subjects with IBD were, on average, deficient in vitamin D. Subjects with Crohn's disease had even lower 25(OH)D levels (11.2ng/mL), while subjects with ulcerative colitis had an average 25(OH)D level (20.2 ng/mL).[20] Crohn's disease involves more of the upper GIT compared to ulcerative colitis, and thus damage in

the upper GIT would more dramatically impact absorption of vitamin D. Jahnsen et al. compared 25(OH)D in 60 patients with Crohn's disease and 60 patients with ulcerative colitis. They found that patients with Crohn's disease had lower concentration of 25(OH)D on average, though the difference was not statistically significant. The lower levels of vitamin D were attributed to malabsorption of the vitamin from the GIT, and the researchers concluded that supplementation with vitamin D should be considered for patients with Crohn's disease.[21] Celiac disease can also interfere with the absorption of vitamin D.[22]

Cystic fibrosis is known to interfere with absorption of fat-soluble vitamins, so it would interfere with the absorption of vitamin D as well. Lark et al. compared patients with cystic fibrosis to a control group (those without CF) and found that vitamin D absorption is lower in patients with CF than in the control group. Although the CF subjects were taking pancreatic enzymes to help with the intestinal absorption of the vitamin D supplementation, their 25(OH)D levels were still lower than the control group (p=0.0012). This suggests that not only is absorption of vitamin D an issue in CF, but CF may also alter some other pathway in its metabolism.[23] One proposed mechanism is an increased clearance of 25(OH)D through increased activity of cytochrome P450 enzymes. Activity of cytochrome P450 enzymes is increased in patients with CF, which could increase the metabolism and clearance of vitamin D in the body.[23,24]

Interference with vitamin D synthesis to an active form can also lead to deficiency. As both the liver and kidneys are needed for calcitriol synthesis, impairment of either hepatic or renal function can result in vitamin D deficiency. Arteh et al. examined 118 patients with chronic liver disease and found that 92.6 percent were deficient in vitamin D, which was defined as serum 25(OH)D levels of less than 32 ng/mL. When the subjects were further broken down into various populations, females had a significantly higher risk of being vitamin D deficient than males, and African Americans had a significantly higher risk of being vitamin D deficient than Caucasians.[25] Chronic kidney disease will also interfere with vitamin D levels. Bansal et al. reported average serum 25(OH)D levels of 10.14 ng/mL in 45 subjects on hemodialysis. Of the subjects investigated, 88.9 percent were concluded to be vitamin D deficient despite supplementation with 400 to 600 IU of cholecalciferol.[26] Holick proposed that the deficiency in active vitamin D in patients with kidney disease is associated with hyperphosphatemia which inhibits production of 1,25(OH)2D, the final, biologically active form of vitamin D produced by the kidneys. Also, the low glomerular filtration rate of patients with kidney disease decreases production of the enzyme 1-alpha-hydroxylase, which is necessary to convert vitamin D to its active form.[27]

Individuals with the conditions mentioned above might want to consider not only vitamin D supplementation but also supplementing with the most appropriate form of vitamin D for their needs. In those who have a problem absorbing vitamin D from the intestine (celiac disease, IBD, nutritional rickets), supplementation with cholecalciferol (vitamin D₃) is pre-

ferred. In a study by Armas et al., it was concluded that chole-calciferol is present in the serum longer than ergocalciferol, and thus is the preferable type of vitamin D to use.[28] Cost and insurance coverage may also be an important consideration when choosing between ergocalciferol or cholecalciferol.

The active form of vitamin D, calcitriol, is available as Rocaltrol®. It does not require further conversion. Calcitriol is indicated in patients with chronic renal dialysis, for secondary hyperparathyroidism in patients with kidney disease and for low calcium in patients with parathyroid gland disorders.[29]

Vitamin D Toxicity

Use of vitamin D supplements and calcitriol may lead to vitamin D toxicity and it is important to educate on the potential harmful effects of hypervitaminosis D. Despite the common belief that more is better, there is no proven benefit for excessive intake of vitamin D, and it can potentially have negative effects with overdose.[31] Symptoms of vitamin D intoxication (VDI) range from increased calcium levels and formation of kidney stones to hardening of soft-tissue.[30-32] In 2010, the IOM also defined the vitamin D Upper Limit (UL), which is the maximum amount of vitamin D that can be ingested before experiencing harmful effects [33] These values can be found in Table 2 as well as comparisons made by NOF.

A retrospective study by Doneray et al. reported on the symptoms of VDI in infants prescribed vitamin D supplementation. In a majority of the patients, the vitamin D supplement was prescribed because patients were not reaching certain developmental markers, including walking, sitting and development of teeth, which is prevalent in rickets.[30] The symptoms that were noted included vomiting, constipation, weight loss, dehydration and hypercalcemia. Some patients even exhibited hypercalciuria and nephrocalcinosis, which are more serious conditions.[30]

Pharmacy Impact

Pharmacists need to be aware of the various guidelines regarding vitamin D supplementation (see additional resources listing at end of article). Individuals may become confused and overwhelmed with the different recommendations and choices of supplementations, causing them to seek the help of a pharmacist for advice on a daily dose specific to their needs. Table 2 lists the current recommendations of the IOM.

Pharmacists need to be aware that these organizations have different recommendations so that they can properly counsel patients coming in with questions. Pharmacists should also understand that vitamin D undergoes several hydroxylations in the body via the liver and kidneys. Therefore, a patient needing supplementation must have adequate kidney and liver function to activate the drug. If unable, a prescription form of vitamin D may be required. Pharmacists play a critical role in the expertise of OTC drugs, and vitamin D is one of these medications. With adequate education, pharmacists can make knowledgeable recommendations to patients to better their overall health.

Additional Helpful Resources

* http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/DRI-Values.aspx
* http://www.nlm.nih.gov/medlineplus/magazine/issues/winter11/articles/winter11pg12.html
* http://nof.org/articles/10

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Table 2. IOM Recommended Daily Allowances (RDA) and Upper Limits (UL) for Vitamin D.[33]

IOM (2010) Vitamin D		
Age	**RDA**	**UL**
Infant (0-6 months)	400 IU/day	1,000 IU/day
Infant (6-12 months)	400 IU/day	1,500 IU/day
Pediatric (1-3 years)	600 IU/day	2,500 IU/day
Pediatric (4-8 years)	600 IU/day	3,000 IU/day
Adolescent & Adult (9-70 years)	600 IU/day	4,000 IU/day
Adults (71+ years)	800 IU/day	4,000 IU/day

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A Review of the Guidelines and Treatment Options for Major Depressive Disorder in Adolescents

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Abstract

Major depressive disorder (MDD) is a disease often underdiagnosed in adolescents. For adolescents in particular, MDD can have far-reaching implications on developmental, social and emotional functioning. Unfortunately, few guidelines detail consistent means by which to evaluate and treat these patients; significantly more information exists that solely pertains to the adult population. Governing bodies such as the American Academy of Child and Adolescent Psychiatry (AACAP) and Resource for Advancing Children's Health (REACH) recommend that primary care physicians be diligent in their psychiatric analyses and follow-ups with young patients who may be experiencing MDD. Both psychotherapy and medications, either as monotherapy or in combination, should be considered when treating MDD. Selective serotonin reuptake inhibitors (SSRIs), particularly fluoxetine, are considered the anti-depressants of choice despite their black box warning pertaining to increased suicidality in children and adolescents. In all cases, benefits of therapy should always be assessed alongside potential risks. Pharmacists can play a significant role in counseling patients on these potential risks and benefits for both the pharmacological and non-pharmacologic aspects of MDD treatment.

Introduction

Major depressive disorder (MDD) is a debilitating disease that greatly affects adolescents, particularly when left untreated. The World Health Organization (WHO) defines adolescence as the growth period between childhood and adulthood when individuals are between the ages of 10 to 19.[1] Major depressive disorder is common in this age group with 11.2 percent of American adolescents suffering from MDD or dysthymic disorder.[2] Dysthymic disorder is a milder form of depression that occurs for at least two years (Table 1).[3] The average length of a depressive episode ranges from two to eight months. The recurrence rate of MDD is anywhere from 20 to 60 percent one to two years after remission, but increases to 70 percent after five years.[4] Although adolescents and adults can both be diagnosed with MDD, adolescents exhibit different signs and symptoms than their adult counterparts.[5] Adolescents may feel physically sick, get into trouble or perform poorly at school, become increasingly irritated or feel misunderstood.[5] In addition, they may become socially withdrawn or suffer from substance abuse.[6] Comparatively, adults may complain of feeling sad, fatigued, or frustrated and may struggle with activities of everyday life.[7]

Major depressive disorder is a complex and disabling disease that can negatively impact all aspects of a patient's life: developmentally, socially and emotionally.[6,8] Any patient suffering from MDD, regardless of age, needs to be treated with medication, psychotherapy or a combination of the two. Like adults with MDD, adolescents are at an increased risk for suicide if their depression becomes too severe.[6] Depressed adolescents are at an even greater risk than depressed adults for completing suicide, which is the third leading cause of death in American adolescents 15 to 19 years of age.[9] In addition to the increased risk of suicide, untreated MDD has long-term social and clinical implications. Adolescents who suffer from milder forms of depression, such as dysthymic disorder, may eventually meet the criteria for MDD as adults if their condition is left untreated.[6] Unfortunately, MDD is often underdiagnosed in this young patient population because they often do not fully meet the diagnostic criteria.[6] Diagnosis may also be complicated by the existence of co-morbid conditions such as anxiety and learning/conduct disorders.[10] Patients who show signs and symptoms of MDD should receive proper diagnosis, psychiatric interventions and adequate therapeutic treatment based on their age and disease severity.[6] Although MDD affects a significant number of adolescents, there is variability between existing diagnostic and treatment guidelines, few medications are currently indicated for MDD treatment in adolescents, and limited research exists in this patient population.[11]

Guidelines for Diagnosis and Treatment

There are a variety of guidelines available for the treatment of MDD in adolescents; however, these documents are inconsistent. Recommendations regarding medication use, psychotherapy and the duration of these therapies vary. The length of psychotherapy and duration of medication use depend on the severity of a patient's MDD. Unfortunately, there are no studies available in adolescents with information regarding which patients should receive therapy past the usual recommendations.[8] Currently, fluoxetine and escitalopram are the only antidepressants approved by the U.S. Food and Drug Administration (FDA) for use in adolescents with MDD.[11]

Guidelines and treatment recommendations are currently available from the American Academy of Child and Adolescent Psychiatry (AACAP) and the Resource for Advancing Children's Health (REACH). The AACAP is a non-profit association whose members aim to treat and improve the quality of life in children and adolescents who suffer from mental health disorders. They provide treatment parameters for a variety of mental health disorders, including MDD.[12] The AACAP published their MDD parameters, which are based on the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), in 2007.[8] Guidelines for Adoles-

cent Depression in Primary Care (GLAD-PC) by REACH were also released in 2007. The GLAD-PC, a North American collaborative, was specifically developed for primary care physicians (PCPs) due to the differences between primary care and specialty care settings. The GLAD-PC: I discuss guidelines for the identification, assessment, and initial management of depression in youth ages 10 through 21. The GLAD-PC: II then outlines the treatment and ongoing management of adolescent depression. Few adolescents with MDD are actually seen by mental health professionals and instead seek help from their PCPs. The GLAD-PC helps PCPs, who may not be familiar with treating MDD in adolescents, properly diagnose and treat these patients.[13]

AACAP Practice Parameters for the Assessment and Treatment of Children and Adolescents with Depressive Disorders
The AACAP states that depression is a spectrum disorder that ranges from subsyndromal to syndromal. To be diagnosed with a syndromal disorder, adolescents must have a change in mood with either a depressed/irritable mood or a loss of interest/pleasure that accompanies a group of other symptoms for at least two weeks. These other symptoms include wishing to be dead, suicidal thoughts/attempts, changes in appetite or sleep and either decreased energy, concentration or self-worth. Although AACAP's diagnostic guidelines were based on DSM-IV, they are still similar to the recommendations in DSM-V (Table 1).[3,8] The AACAP recommends that physicians develop a relationship with their patient, his or her family, school personnel and other health care providers. The academy also suggests that physicians screen young patients at regular office visits to identify depressive disorders. If screening suggests the patient may be suffering from a depressive disorder, further evaluation is warranted including an assessment about harm to the patient or others. Additionally, this evaluation should include a family history of depressive disorders, ongoing or past negative events, such as abuse or divorce of parents and available support for the patient.[8]

Treatment with medication should always include an acute and continuation phase. Maintenance treatment may also be

Table 1. Adapted from the DSM-V.[3]

DSM-V Diagnostic Criteria for MDD in Adults and Adolescents	
Criteria A	A patient must have **at least five** of the following symptoms occurring during the same two-week period and represent a change from previous functioning. One of the symptoms must either be depressed mood OR loss of interest/pleasure. 1) Depressed mood most of the day nearly every day. 2) Marked decrease in interest/pleasure most of the day nearly every day. 3) Significant weight loss or gain (5% of body weight in a month) or decrease in appetite nearly every day. 4) Insomnia or hypersomnia nearly every day. 5) Psychomotor agitation or retardation nearly every day (observed by others). 6) Fatigue or loss of energy nearly every day. 7) Feelings of worthlessness or excessive/inappropriate guilt nearly every day. 8) Diminished ability to think or concentrate or indecisiveness nearly every day. 9) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan.
Criteria B	Symptoms cause clinically significant distress/impairment in social, occupational, or other aspects of life.
Criteria C	Episode not attributed to physiological effects of substance abuse or another medical condition.
Criteria D	The occurrence of the major depressive episode cannot be explained by schizophrenia or a schizophrenia-like illness or another psychotic disorder.
Criteria E	There has never been a manic or hypomanic episode.

appropriate in some patients. Treatment during the acute phase is to help relieve symptoms, while continuation treatment is to prevent relapse and to strengthen the acute phase. Maintenance therapy is recommended for patients who have a more severe or chronic disorder to prevent recurrence. Treatment at every stage should include patient and caregiver education on MDD, supportive management, and family/school involvement. Both parents and patients should be a part of the decision-making process for treatment. Adolescents with uncomplicated or brief depressive symptoms can often be successfully treated with education, case management and supportive care (psychotherapy) for four to six weeks. Patients who have a limited response to nonpharmacologic therapy or those with more severe depression may require both psychotherapy and antidepressant medications. The AACAP defines response to treatment as having no symptoms or having a significant reduction in depressive symptoms for at least two weeks.[8] Both psychotherapy and antidepressants can be used as monotherapy. Research attempting to prove a benefit exists in patients using combination therapy has been inconclusive.[14] However, clinicians state that patients do respond better to combination therapy; therefore, AACAP suggests patients receive both psychotherapy and medications, especially if they have moderate to severe or refractory MDD. The AACAP recommends patients use fluoxetine because it is indicated for use in adolescents (Note: these guidelines were published before escitalopram was an indicated therapy). Studies with selective serotonin reuptake inhibitors (SSRIs) other than fluoxetine had not shown a significant difference in treatment response compared to placebo when these guidelines were written.[8]

The doses of SSRIs used in adolescents are similar to adult dosages. Low doses should be given initially and then titrated up to the lowest effective dose. Prescribing physicians should reassess the patients every four weeks and adjust doses when necessary. It is recommended that patients be treated for six to 12 months to avoid relapse. Physicians should also evaluate their patients to see if they are candidates for longer use; candidates include those with severe or refractory depression. Somatic treatments, such as electroconvulsive therapy or transcranial magnetic stimulation, in addition to pharmacotherapy and psychotherapy, may be necessary in patients with psychosis, seasonal depression or bipolar disorder. Moreover, comorbid psychological and physiological conditions should also be appropriately treated.[8]

Guidelines for Adolescent Depression in Primary Care
The recommendations from the GLAD-PC: I state that the PCP identifies adolescent patients who are at risk for depression and systematically monitor them for the development of a depressive disorder. The PCP should specifically assess psychosocial function in adolescent patients, as altered function can be an early sign of depression. Risk factors include personal or family history of psychiatric illness, substance abuse and suicidal behavior. Adolescents under psychosocial stress due to abuse, neglect or other traumatic events are also considered at increased risk for depression. To assess and diagnose patients, the PCP should evaluate both high-risk patients and patients who describe emotional problems

as their chief complaint. Assessment should include direct interviews with the patient as well as family members or caregivers. The GLAD-PC also recommends diagnosis of depression based on the diagnostic criteria described in DSM-IV or in International Classification of Diseases, 10th Revision (ICD-10). During initial management, the PCP should educate the patient and family members about depression and its symptoms. A treatment plan should be established and goals should be set individually for key areas of function for the patient: home, school and peer settings. All management must include a safety plan that establishes an emergency contact in case of increased suicidality or crisis-type situations resulting from the depressive symptoms or treatment. The GLAD-PC notes that a safety plan should be established early because safety concerns are highest during diagnosis and initial management. The PCP should involve a concerned third party, such as a school nurse or other adult that can provide adequate support and supervision. It is also recommended that all materials that could cause serious harm or death be removed as a measure of precaution.[15]

According to GLAD-PC: II, the PCP should provide a six to eight week period of active support and monitoring for patients diagnosed with mild depression before making a treatment recommendation. The PCP should monitor patients every one to two weeks through follow-up phone calls in addition to frequent office visits. The PCP can provide support by making recommendations for exercise or leisure activities, peer support groups and patient self-management goals. Educational materials should also be provided to the patients and their families at this time.[16] If patients continue to present with symptoms, treatment with an SSRI antidepressant or psychotherapy should then be recommended. Fluoxetine is considered first-line treatment for all adolescents ages 10 through 21. Escitalopram is considered first-line treatment for adolescents ages 12 through 21.[16] Immediate treatment is recommended for adolescents with moderate to severe depression. Additionally, consultation with a mental health specialist should be considered in cases of adolescents with moderate/severe depression, coexisting substance abuse or psychosis. If a referral is made, the roles and responsibilities of both the PCP and mental health clinician need to be discussed and agreed upon by the involved clinicians, the patient and the patient's parents/guardian. It is important to note that the PCP should continue to follow-up with the adolescent after the referral.[17]

The guidelines note that appropriate psychotherapy methods include cognitive behavioral therapy (CBT) and interpersonal therapy (IPT). Cognitive behavioral therapy focuses on the patient's thoughts and behaviors to improve their mood. Parents or caregivers may be included in sessions of CBT. Key components of this therapy include incorporation of pleasurable behavior, reducing negative thoughts, and decreasing feelings of hopelessness by improving problem-solving skills. IPT focuses on interpersonal problems that may act to either cause or worsen depression. Goals of therapy include addressing specific interpersonal problems while improving interpersonal problem-solving skills and communication skills.[18] Parents and caregivers are invited to partici-

pate during specific phases of IPT, including the first session, during the middle phase of treatment and at the end of treatment.[17,18]

The PCP should reassess diagnosis and initial course of treatment if no improvement is seen within six to eight weeks of treatment for moderate to severe depression. Additionally, a mental health consultation should be reconsidered if there is no improvement noted after initial treatment or only partial improvement is seen after all primary care therapeutic approaches have been attempted. A reduction in symptoms of depression, improved ability to function and reports of improvement by the patient or parent/caregiver are all considered indicative of improvement. Several diagnostic aids in addition to DSM-IV and ICD-10 are mentioned in the GLAD-PC toolkit that can assist in reassessing patients and quantifying a reduction in symptoms. The Columbia Depression Scale—Teen Version is a survey that consists of yes or no type questions and incorporates inquiries about suicide ideation and attempts. The scale is based on a point system where "yes" is worth one point and "no" is worth zero points. There are two versions of the survey—one for parents and one for the adolescent. The scores are then assigned to the chance of depression, ranging from very unlikely to highly likely. In addition, the six question Kutcher Adolescent Depression Scale (KADS) is scored to indicate if a patient is "possibly depressed" or "probably not depressed." Moreover, a modified version of the Patient Health Questionnaire, 9th Revision (PHQ-9) is available to assess adolescent depression (note: research has not been conducted to validate the modifications). Modified PHQ-9 consists of a survey format that incorporates the frequency of symptoms (i.e. "not at all" through "nearly every day"). Points are assigned to the patient's responses that rank the severity of depression from mild to severe.[16]

After reassessing the patient, the PCP should address the choice and efficacy of initial treatment. If the patient does not respond to the maximum therapeutic dose of an SSRI antidepressant, treatment with a different SSRI antidepressant should be considered. The GLAD-PC toolkit for PCPs includes SSRIs not FDA-approved for adolescents (i.e. sertraline, citalopram, fluvoxamine, paroxetine) as alternatives.[16] If only psychotherapy or only antidepressant therapy was initially utilized, the clinician should consider adding the other therapy to the patient's treatment plan.[17] If the patient fails two trials of treatment with an SSRI and a course of CBT or IPT, the PCP should consult a mental health specialist to recommend a second-line medication such as citalopram or sertraline. If a patient fails a third medication trial, the PCP should reevaluate their diagnosis and consider a combination of medications.[16] Increasing the initial SSRI antidepressant dose above FDA-approved ranges is also suggested as a possible consideration for patients who only partially respond to therapy. The guidelines do not specify if this is a last-line option, but recommend that the dose be increased in consultation with a mental health professional. Assessments should include the presence of comorbid conditions such as substance abuse or bipolar symptoms that may affect treatment.[17]

According to GLAD-PC, ongoing management should include the tracking of goals and treatment outcomes. Goals of treatment include both an improved ability to function and cessation of depressive symptoms. Moreover, the patient's level of function should be assessed in various environments (i.e. home, school, and peer settings). Patients should be seen within one week of beginning treatment to initiate such tracking. Both GLAD-PC and AACAP experts recommend that antidepressant therapy should be continued for six to 12 months after complete resolution of depressive symptoms. The GLAD-PC cites AACAP in the recommendation that patients may be monitored for up to two years if patients suffer from recurrent depressive episodes.[8,17] If treatment includes an SSRI antidepressant, the PCP should monitor the patient for adverse events. The GLAD-PC references the FDA's recommendation for monitoring children and adolescents using antidepressants for clinical worsening, suicide risk and changes in behavior. These guidelines note that the optimal frequency of monitoring is controversial.[17]

Pharmacological Treatment Options
Selective serotonin reuptake inhibitors are most commonly prescribed to treat depressive disorders due to their effectiveness over older generations of antidepressants such as the tricyclic antidepressants (TCAs). SSRIs directly inhibit the adenosine triphosphate (ATP) dependent carrier in presynaptic neurons. Without a functional reuptake pump, serotonin (5-hydroxytryptamine [5-HT]) is not broken down or recycled to produce more 5-HT. Instead, there will be an accumulation of this particular neurotransmitter in the synaptic cleft for continuous stimulation of serotonergic neurons. However, this process has no correlation to the duration of therapy since the onset of action for all antidepressants is typically delayed. If this were the case, adolescents would feel immediate relief within three days. Typically, maximum improvement in mood can take place within two weeks.[19] Another mechanism suggests that SSRIs induce desensitization of somatodendritic and terminal 5-HT1$_A$ autoreceptors, proteins responsible in inhibiting the release of 5-HT and other neurotransmitters from the presynaptic neuron.[20] Overstimulation of the autoreceptors would cause this desensitization. By attenuating the negative feedback responsibilities of these autoreceptors, 5-HT will accumulate to a greater extent, leading to an antidepressant response.

Side effects associated with SSRI use occur due to the inhibition of other signaling transduction pathways; thus, leading to additional physiological responses.[20] Selective serotonin reuptake inhibitors generally improve mood, but they can also cause one to experience suicidal thoughts due to the inhibition of dopamine neurotransmission. Increasing concentrations of 5-HT with SSRIs downregulates dopamine receptors in the prefrontal cortex, the area of the brain responsible for cognitive behavior, personality, expression, decision-making and moderating social behavior.[20] Compromising mesocortical dopaminergic pathways could trigger impulsive and aggressive behavior toward oneself (e.g. suicide). To reverse the downregulation of dopamine receptors, researchers are currently investigating 5-HT2$_C$ receptors, proteins localized in the dorsal striatum, which are responsi-

ble for modulating striatal and prefrontocortical dopamine concentrations.[20] By discovering the correlation between these receptors and dopaminergic tone, scientists can better treat conditions such as depression.

Black Box Warning

In 2004, the FDA directed all manufacturers of antidepressants to add a black box warning (BBW) to SSRI labeling to alert health care providers of the increased risk of suicidality in children and adolescents being treated with these agents. The FDA also directed manufacturers to include information from pediatric studies regarding suicide risk in the labeling.[21] While suicide risk is highlighted for children, adolescents, and young adults, labeling states that all patients taking antidepressants should be monitored for clinical worsening, suicidality, or altered behavior during the initial months of treatment and during any dosage changes.[22,23] According to the warnings, the clinical need of the medication should be weighed against the clinical risks in any child, adolescent or young adult patient who is being considered for antidepressant therapy.[21]

Controversy still exists over this BBW. Some studies have shown statistically significant increases in suicidal thoughts and actions in adolescents on SSRIs, while others have not.[24,25,26] A study by Gibbons and colleagues showed that adolescent patients on SSRIs had a lower risk of suicide compared to patients on placebo.[26] Additionally, the government-funded Treatment for Adolescents with Depression Study (TADS) found that patients who received combination therapy of medications and psychotherapy had a lower suicide risk.[24] Interestingly, early in the trial, 29 percent of patients had suicidal thoughts. At the end of the study only 8 percent of patients on combination therapy had suicidal thoughts, compared to 15 percent of patients taking fluoxetine alone.[24] In another study, Ma and fellow researchers found that while the number of prescriptions for antidepressants is increasing, fewer patients are receiving them in combination with psychotherapy.[25] The AACAP recommends adolescents receive both medication and psychotherapy. This treatment combination is beneficial because it provides an opportunity for patients to develop coping skills and helps them develop a plan to continue treatment. The decrease in psychotherapy utilization may be a confounding factor contributing to the increased suicide rate associated with SSRIs.[8]

Some practitioners argue that the BBW discourages doctors from prescribing antidepressants to adolescents who really need to be treated with medication. Others argue that the risk of suicide, if MDD is left untreated, is higher than if a patient was placed on an SSRI. Regardless of reasoning, there is need for more research to discover whether or not suicidal activity is definitively linked to SSRI use in adolescents.[23]

Because a warning exists, the AACAP suggests that all patients receiving SSRIs be monitored for suicidal thoughts and actions. Patients with an especially high risk of suicide should be monitored particularly closely. These patients include those suffering from bipolar disorder, substance abuse, sexual abuse and patients with suicidal tendencies or a family history of suicide. The AACAP supports the FDA recommendation that patients be seen once a week for the first four weeks of therapy and then biweekly thereafter. Monitoring can be done via telephone or by a face-to-face meeting.[8]

SSRI-Resistant Depression

Some adolescent patients may not see any improvement after initial treatment with an SSRI. The National Institute of Mental Health funded a multi-site, clinical study to investigate treatment of adolescents with SSRI-resistant depression (TORDIA) that was conducted from 2000-2006.[27] The purpose of the study was to evaluate the efficacy of four different treatment strategies in adolescents who did not respond to initial treatment with an SSRI. Three hundred and thirty-four adolescents, ages 12 to 18 years, who had not responded to two months of initial treatment were randomized to one of the four treatment groups. Treatment groups included: switch to an alternate SSRI, switch to the selective serotonin-norepinephrine reuptake inhibitor (SSNRI) venlafaxine, switch to a new SSRI in combination with CBT, and switch to venlafaxine in combination with CBT. The groups treated with both venlafaxine and CBT or a new SSRI in combination with CBT had a higher rate of clinical response than the groups that did not incorporate CBT. There was no difference in clinical response between the adolescents who switched to a new SSRI and the adolescents who were treated with venlafaxine. However, venlafaxine was associated with a greater increase in diastolic blood pressure, pulse rate and skin problems. The TORDIA study was designed to detect a 10 percent difference between groups at a power of 80 percent for a sample size of 400 participants. Brent and colleagues stated that the sample size was not met due to a public health advisory that the FDA issued to health care providers regarding risk of suicidality in pediatric patients taking SSRIs. The warning was issued at the midpoint of the study in 2003. The authors noted that recruitment of participants became difficult when the concern about suicide risk in pediatric patients taking SSRIs increased; thus, the overall use of SSRIs declined.[27,28] Although the results were not statistically significant, TORDIA still provided clinically significant data regarding treatment options for adolescents who do not respond to initial SSRI treatment.

Special Considerations with Antidepressant Treatment in Adolescents

There is high variability in adolescent placebo response, which limits interpretation of clinical trials for pharmacologic treatment of adolescents with MDD. Trials comparing antidepressant treatment to placebo in adolescents have reported a wide range of placebo response from lower rates of approximately 20 percent to higher rates of 70 percent.[29-32] Variable placebo response to antidepressants is not restricted to the adolescent population. Reif and colleagues recently conducted a meta-analysis analyzing 96 studies and 9,566 patients (excluding children). The analysis did not differentiate between different classes of antidepressants. In patients taking antidepressants versus placebo, it was determined that the placebo response accounted for 68 percent of the effect in the drug groups. However, variations in the depression diagnosis (i.e. type and severity) and study design

were noted as cause for variation in recorded placebo responses.[33] Therefore, in future research, the effect of placebo treatment in depressed adolescents will be a necessary consideration. It is important to note that research regarding pediatric patients is often limited by small sample sizes due to fear of complications or violation of ethical standards.

Another important consideration in pharmacologic treatment is the developmental differences between adolescents and adults that can impact various pharmacokinetic parameters. In practice, pediatric dosing is often derived from the adult dose and adjusted according to body weight or body surface area for off-label uses of medications. Because this method does not account for developmental differences, it places patients at risk for either sub-therapeutic dosing and lack of effect or supra-therapeutic dosing and adverse events.[34] According to a systematic review conducted by Moreno and colleagues, adolescents may, theoretically, experience higher plasma concentrations of lipophilic drugs like antidepressants and antipsychotics because they have a higher body water/adipose ratio (i.e. lower percentage of body fat) than adults.[35] However, it is also believed that hepatic cytochromes have higher activity in adolescents around puberty than adults. Once puberty is reached, sex hormones are believed to compete for hepatic enzymes, meaning higher doses of antidepressants may be required to avoid sub-therapeutic dosing.[35]

Adolescents qualifying for discontinuation of therapy that are currently taking SSRIs or SSNRIs must be gradually weaned off their medications over a four-week time period.[36] Patients who are suddenly taken off their medications can experience discontinuation symptoms. The symptoms are characterized by a severe withdrawal effect resulting in headaches, nausea, tremor, anxiety and agitation. Research has indicated that the magnitude of withdrawal is inversely proportional to the half-life of the drug.[36] A shorter half-life would result in a faster elimination rate and more episodes of discontinuation symptoms. Fluoxetine, which has a very long half-life (one to three days after acute administration and four to six days after chronic administration), evokes the least amount of withdrawal symptoms for patients. On the contrary, other SSRIs (i.e paroxetine and sertraline) and SSNRIs (i.e venlafaxine, duloxetine) evoke more severe withdrawal symptoms.[36,37] Venlafaxine, with a short half-life of three to 13 hours, is rarely indicated for adolescents with depressive disorders because it tends to cause more frequent and robust withdrawal symptoms. In the literature, SSNRIs have not demonstrated better effectiveness than SSRIs.[36] Additionally, since they cause more adverse reactions than SSRIs, SSNRIs should be avoided and not recommended as first-line agents in adolescent patients with depressive disorders.

Thoughts on Adolescent Depression

In 2003, the American Psychological Association (APA) issued a press release stating that adolescents who suffer from depression are susceptible to relapses of symptoms in adulthood. According to APA, intervention and prevention of adolescent depression are important to avoid such relapses.[38]

In 2005, the National Institute for Health and Clinical Excellence (NICE) and the National Collaborating Centre for Mental Health issued a press release stating that new standards had been developed regarding the treatment of depression in adolescents. According to NICE, mild depression should not be treated with antidepressants, and psychological therapy should be first-line treatment for moderate to severe depression. If antidepressant therapy is initiated, it should be provided along with psychological therapy. Health care professionals in close contact with adolescents should be trained to detect symptoms of depression. The standards also mentioned that there is the possibility of concurrent depression in parents that would need to be addressed in order to ensure effective treatment of their child's depression.[39]

In 2006, APA issued a press release highlighting a report regarding the gap in care for many adolescents. The gap was associated with limited access to appropriate services for mental health issues. The report called for research to further investigate the efficacy of treatments for depression as well as what doses and dosage intervals are appropriate in the adolescent population. The need for further research in the various combinations of pharmacologic treatment and psychotherapy was also highlighted. The American Psychological Association's report stressed the importance for research to investigate the role of outside influences such as family members or school employees on depressed adolescents' adherence to treatment. Additionally, APA cited a need for increased collaboration among U.S. federal agencies that fund treatment research as well as public disclosure of safety and efficacy data from the treatment research.[40]

The Pharmacists' Role

Pharmacists have an important role in monitoring patient compliance and safety with antidepressant medications. It is imperative to inform patients to not abruptly discontinue their therapy. Adolescents and their parents should be informed of the aforementioned risks due to sudden discontinuation (i.e withdrawal symptoms). Discontinuation could result in a longer duration of therapy to not only correct the withdrawal symptoms, but to also treat the original depression state. Patients and their caregivers should also be advised that the physician will make all necessary medication adjustments as needed. Modifying medication therapy by oneself should be strictly prohibited; instead, one must consult with the physician. Since adolescents typically have faster metabolism than adults, they can experience even more severe withdrawal symptoms.[36] However, these effects and risks can be avoided with appropriate clinical management.

Pharmacists can also play an important role in providing nonpharmacologic counseling to adolescents experiencing recurrent episodes of suicidal ideation by encouraging patients and/or their parents to attend regular psychotherapy sessions. Furthermore, it is imperative to look for any signs of bipolar disorder, schizophrenia and/or a history of MDD in family members via examining family health history. The pharmacist should work collaboratively with the primary

physician to get any health information needed. If a family history of mental health disorders exists, then this may be a contributing factor to the patient's depression. Explaining this possible genetic link to patients could help to further the patient's understanding of their disease. Additionally, patient noncompliance of medication therapy is an area where pharmacists can make very positive interventions. Patient noncompliance can be due not only to lack of understanding about the importance of taking these antidepressants on a regular basis, but also can be due to the possible side effects from antidepressants. Thus, face-to-face follow-up visits with the pharmacist should be highly encouraged. These visits could occur weekly or biweekly. Seeing both a pharmacist as well as a physician could help to ensure efficacy and decrease the risk of adverse effects of antidepressant medications. It is imperative to also counsel parents about the importance of compliance with antidepressant medications, since caregivers/parents have great influence on an adolescent's life. Upon dispensing medications, pharmacists should also distribute medication guides, so that the patient can be fully aware as to what their therapy entails, and encourage the patient to call with any questions or concerns.[41]

Conclusion

Although guidelines exist for the treatment of MDD in adolescents, these reports vary and are oftentimes not utilized in clinical practice. Treatment is inconsistent among physicians, and prescribers often choose to prescribe medications that are not indicated for the treatment of MDD in adolescents. More research needs to be conducted to further clarify the guidelines, add additional therapies to treatment options and to end the controversy that exists over whether or not to treat adolescent MDD patients with fluoxetine or escitalopram. Increasing the amount of patient and parent counseling will hopefully lessen the fear of adverse effects and social stigma concerns that surround antidepressants, allowing adolescents to receive the treatment that they need for MDD.[20] There are risks and benefits with taking medications to treat MDD; however, the benefits more often outweigh the risks. Effectiveness of medications can be achieved if dosing is gradually titrated, assuming that the patient is responding well to therapy. Most importantly, patients should avoid high-risk agents such as SSNRIs.[41] Finally, it is important for health care providers to communicate with one another and with their patients to address these risks and benefits for antidepressant treatment in adolescents. Due to their accessibility, pharmacists play a particularly important role in educating patients and caregivers on the importance of medication adherence and monitoring for signs of suicidal ideation.

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Phenoconversion: Drug-Drug-Gene Interactions

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Abstract
Based on the extensive, poor, intermediate and ultrarapid phenotypes of patients, inferences may be made relative to drug metabolism, ultimately leading to changes in therapeutic drug choice or dosing. Phenoconversion is a phenomenon that occurs when an individual's drug metabolizing capacity is altered due to the combination of a drug-drug interaction and a drug-gene interaction. Phenoconversion can affect pharmacokinetics as well as pharmacodynamics. Some examples of phenoconversions include amiodarone-warfarin, duloxetine-codeine, rifampin-clopidogrel, and rifampin-warfarin. Pharmacists must consider phenoconversion in cases of multi-drug therapy.

Introduction/Background
Pharmacogenomics (PGx), in relation to drug metabolism, stems from the basics of the human genome itself. It begins with the genotype (specific inherited alleles, forms of a gene), which, along with other factors, leads to the phenotype (expression of the individual gene via physical traits or physiological functions).[1] Relative to the deoxyribonucleic acid (DNA) code are polymorphisms, which are genetic mutations found in more than 1 percent of the population. Most often these mutations are single base substitutions known as single nucleotide polymorphisms (SNPs).[1] With SNPs, resulting variant genes and subsequent expressions are what define an individual's inherent capabilities, such as those related to drug metabolism. Based on the occurrence of SNPs and other mutations, some individuals will have "normal" protein function, while others may not.[2] Some of the proteins of interest function to metabolize drugs, therefore when their function is altered or absent, two aspects of drug metabolism can change dramatically the extent of drug metabolism and the rate of drug metabolism. In general, a "wild-type" allele (normal gene) will code for the typical or normal enzyme, and an individual with this type of allele would be considered an extensive (normal) metabolizer (EM; NM) of drugs which are substrates for the enzyme. In contrast, individuals may receive variant alleles, which result in metabolism phenotypes of poor (PM), intermediate (IM), or ultrarapid (UM). Based on these phenotypes, inferences may be made relative to drug metabolism, ultimately leading to changes in therapeutic drug choice or dosing (e.g., choice of antiplatelet medication or alteration of dose for a chemotherapeutic agent).[2,3]

Pharmacogenomics as explained above has had greater uptake in recent years, resulting in more proactive genetic testing occurring prior to drug administration in an attempt to decrease or avoid adverse drug reactions that are linked to variant alleles. However, while PGx is starting to be applied in practice today, the problem of phenoconversion has presented itself as another piece of the puzzle. Phenoconversion is an alteration in an individual's drug metabolizing capacity due to the combination of a drug-drug interaction and a drug-gene interaction. In other words, an individual's phenotype is transformed as a consequence of a drug-drug-gene interaction (DDGI) (e.g., an IM being converted to a PM). One of the interactions, the drug-drug interaction, is familiar to pharmacists since individuals are often put on multidrug therapies that may lead to additive effects or possible toxicities either by synergistic or antagonistic mechanisms. The drug-gene interaction component of phenoconversion is described by the previously discussed definition of pharmacogenomics and different metabolic "intrinsic" (inherited) phenotypes.[1-3] The consequence of a DDGI is altered pharmacodynamics and/or pharmacokinetics. Pharmacodynamic (PD) interactions occur when one drug alters the response to another drug through alteration in drug receptors without the influence of a change in drug concentration. Pharmacokinetic (PK) interactions occur when a drug interferes with the absorption, distribution, metabolism and/or excretion (ADME) of another drug, here altering the concentration of the original drug.[3] Either one of these situations can create phenoconversion, but ultimately an individual's genotype will no longer match their predicted phenotype. A DDGI occurs when the first drug is given to an individual with altered drug metabolism due to a variant genotype (drug-gene interaction) followed by an additional drug that alters the PD or PK of the first drug (drug-drug interaction). Now, instead of a drug-gene interaction alone or a drug-drug interaction alone, we must consider a DDGI, and this phenoconversion can result in increased or decreased drug concentrations with subsequent adverse effects or therapeutic failures, respectively. The following are individual examples of phenoconversion.

Amiodarone and Warfarin
Warfarin is a frequently prescribed medication for anticoagulation therapy and is commonly given to patients that have atrial fibrillation, a heart valve replacement or a history of clotting for prevention of stroke and other sequelae. Warfarin is manufactured as a racemic mixture, where 50 percent exists as the S-isomer and the remainder as the R-isomer. The S-isomer, however, is almost five times more potent than the R-isomer, resulting in this form's more extensive role in warfarin's therapeutic activity.[1] As such, the cytochrome P450 enzyme that is responsible for metabolizing warfarin's S-isomer, CYP2C9, plays a significant role in determining the dose that will be required in a given patient.[1,4] Those individuals with a *1/*1 genotype are considered to be more extensive in their ability to metabolize warfarin. Individuals with some combination containing a *2 or *3 allele (e.g., *1/*2, *2/*2, *2/*3, etc.) have reduced enzyme activity, meaning that warfarin's clearance is decreased and warfarin will linger in the body for a longer time as a result of a longer half-life. A decrease in the clearance of

warfarin of approximately 30 to 40 percent can be expected when an individual has a *2 allele, with an individual who is homozygotic (*2/*2) having a greater decrease in clearance as compared to the heterozygotic individual (*1/*2). The effects of CYP2C9 allele variation on the clearance of warfarin is even more pronounced in individuals with a *3 allele, where a homozygotic individual may have a decreased clearance approaching 80 to 90 percent. The *2 and *3 alleles are most frequently found in those of European descent. These phenotypes are not categorized in the typical manner as extensive metabolizers, intermediate metabolizers, or poor metabolizers, but instead can be thought of as existing on a continuum. In this manner, a *1/*1 genotype would be comparable to an extensive metabolizer with efficient metabolism and a *3/*3 individual would resemble a poor metabolizer. Other alleles associated with decreased enzyme activity include CYP2C9*5, *6, *8, and *11, which are found most commonly in the African American population.[4] When another drug that utilizes this CYP is prescribed for a patient that is already taking warfarin, there is a potential for decreasing the enzyme's ability to metabolize warfarin, thereby resulting in a need to adjust the dose accordingly (Table 1).

In order to ensure that a patient is receiving the correct dose of warfarin for their phenotype, that patient's INR, or international normalized ratio, is monitored closely. When measuring an INR, a small collection of blood is analyzed in order to determine the amount of time it takes for that patient's blood to clot. A typical healthy individual that is not taking warfarin could expect an INR value of approximately 1, while those consuming warfarin would have higher INR values. When a patient has suffered from or is at risk of developing a clot, it is necessary to keep the INR value between 2 and 3. In individuals that have had a mechanical heart valve placed, an INR between 2.5 and 3.5 is desired. The INR must be monitored by a health care professional regularly, as many medications, foods and drinks can impact the anticoagulant effects exhibited by warfarin.[5]

For example, ML is an 80-year-old woman who has been taking warfarin for four years after she developed a deep vein thrombosis. Her INR has remained steady at 2.7 while on her prescribed dose of 3 mg daily throughout those years of use. Her genotype is *CYP2C9*2/*3*, indicating that she has decreased warfarin metabolism, thus defining a drug-gene interaction. Here, ML has a 60 percent decrease in the clearance of warfarin when compared to the normal wild-type, *1/*1 genotype.[1] While not specifically defined for CYP2C9, ML may generally be considered an intermediate metabolizer on the continuum from *1/*1 to *3/*3. Recently, ML was hospitalized to treat a ventricular arrhythmia. During this time, she was started on amiodarone.

Amiodarone also utilizes the CYP2C9 enzyme and is known to be a moderate inhibitor of this enzyme. This causes a reduction in warfarin clearance by 50 to 80 percent.[6] Enzyme inhibition is primarily caused by the metabolite, desethylamiodarone, which is a much more potent inhibitor of CYP2C9 than the parent amiodarone form. Furthermore, it has been demonstrated that the degree to which CYP2C9 is inhibited is related to the amiodarone dose that is administered.[4] Therefore, patients taking higher doses of amiodarone would experience a greater decrease in CYP2C9 function and would resultantly require a lower dose of warfarin.

In the case involving ML, phenoconversion would effectively move ML along the continuum from resembling an intermediate metabolizer to resembling a poor metabolizer.[1] Consequently, ML would have higher concentrations of warfarin in her body, thus potentiating the anticoagulant effects of her

Table 1. The *CYP2C9* "warfarin dosing continuum." The *2 and *3 variant alleles impart decreased warfarin metabolism (clearance), necessitating decreased warfarin maintenance doses.[4]

VKORC1	*CYP2C9*[a]					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG[b]	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg

[a] *1 – normal CYP2C9 activity; *2 – somewhat decreased CYP2C9 activity; *3 – greatly decreased CYP2C9 activity.
[b] The common VKORC1 genotype, imparting "normal" warfarin pharmacodynamics.

medication, as can be verified through an increase in her typically stable INR from 2.7 to 5.3. This places ML at an increased risk for bleeding.[4,7,8]

The original drug-gene interaction is a component of the overall interaction with the addition of amiodarone. Due to the decreased warfarin metabolism rate as a result of the DDGI, it is recommended that on the third or fourth day following amiodarone's inclusion in the patient's medication regimen, the usual warfarin dose should be decreased by one-third to one-half. In ML's situation, that means that the dose should be decreased from 3 mg daily to 1.5 to 2 mg daily. Her INR should be monitored closely during this time until stabilized.[8]

Duloxetine and Codeine

SK, an African American woman, brings a prescription for acetaminophen 300 mg/codeine phosphate 30 mg to the pharmacy because she has been having severe back pain for the past three days. Previously, as part of a pharmacy program emphasizing personalized medicine, SK provided a DNA sample via a cheek swab. The laboratory working with the pharmacy tested for many different genes related to drug metabolism; this included the gene coding for the drug metabolizing enzyme CYP2D6, for which SK had the genotype of *CYP2D6*4/*17*, indicating that SK is an intermediate metabolizer. From this genetic test, it is determined that SK may not effectively metabolize codeine to its active metabolite, morphine.[9] The doctor writes the acetaminophen 300 mg/codeine phosphate 30 mg prescription for one tablet every four hours as needed.[10] When checking the prescription, the pharmacist discovers that SK is also prescribed duloxetine for her depression. This is a potential drug-drug-gene interaction because duloxetine is a moderate inhibitor of CYP2D6 and could therefore affect the metabolism of codeine, which can result in inadequate pain relief for SK.[6]

The phenotype of the patient for the *CYP2D6* gene is determined through an activity score, which is calculated by adding the scores of the two alleles of the individual's genotype. The alleles *1, *2, *27, *33, *45, *46, *39, *48, and *53 have normal activity and are given a score of 1. Reduced function alleles include *9, *10, *17, *29, *41, *50, *54, *55, *59, *69, and *72; these alleles have an activity score of 0.5. All other, currently identified alleles are considered non-functional and have an activity score of 0.[9] Ultrarapid metabolizers of codeine have an activity score over 2, which can occur when there are more than two functional alleles present, as some individuals have two or more copies of the gene. Normal metabolizers have an activity score between 1 and 2, intermediate metabolizers have a score of 0.5, and poor metabolizers have a score of 0.[10] Table 2 summarizes these activity scores and the metabolizing function of various alleles of *CYP2D6*. SK would have an activity score of 0.5, receiving a score of 0 from the *4 allele and 0.5 from the *17 allele; her phenotype would therefore be an intermediate metabolizer.

As a moderate inhibitor of CYP2D6, duloxetine could prevent codeine from being metabolized to morphine and prevent it from having a therapeutic effect. A moderate inhibitor of a CYP enzyme is defined as causing a twofold or more increase but less than fivefold increase in area under the curve (AUC) of the enzyme's substrate.[6] In the case of SK, the duloxetine could inhibit the CYP2D6 enzyme, a product of the *17 allele, which already has reduced activity; this would inhibit codeine conversion to morphine, eliminating most of the analgesic effect provided by the medication. SK would undergo a phenoconversion from an intermediate metabolizer of codeine to a poor metabolizer if she were to take duloxetine and codeine concomitantly. For instance, her metabolism of codeine may be considered similar to someone with the *CYP2D6*4/*4* genotype, resulting in little or no therapeutic benefit because the drug is not metabolized to its active metabolite (codeine). [9]

Table 2. Examples of *CYP2D6* Variants.[a]

Function	Example Alleles (Activity score)[b]
Normal	*1[c], *2, *27, *33, *35, others (1)
Decreased	*17, *29, *41, *49, *50, others (0.5)
Lost	*3, *4, *5, *6, *7, others (0)

[a] Adapted by permission from Macmillan Publisher Ltd: Clinical Pharmacology & Therapeutics 2012;91(2):321-6, Crew et al., copyright 2012.

[b] The activity score relates formation of metabolite to an individual's genetics, with those producing more metabolite being assigned a higher activity score.

[c] Designated as the "wild-type," and the most frequently occurring form with normal function.

If codeine is going to be used in patients taking drugs that moderately inhibit the CYP2D6 enzymes such as duloxetine, the patient should be carefully monitored to determine whether or not pain relief is adequate. There are also alternative therapy options for pain management that do not involve the CYP2D6 metabolism pathway and therefore would avoid phenoconversion due to concomitant therapy of codeine with duloxetine. Fentanyl, oxymorphone, hydromorphone and morphine are among the analgesics not metabolized by CYP2D6. Tramadol, hydrocodone and oxycodone should be avoided because they are also metabolized by CYP2D6 to their active forms and could potentially be affected by the inhibitory effects of duloxetine. In addition, there are non-opioid based pain medications such as NSAIDs and acetaminophen that do not require CYP2D6 for activation or metabolism. The choice of alternative therapy should be made based on pain severity relative to each individual.[9] In the case of SK, the pharmacist called the prescriber, who agreed to switch the prescription from acetaminophen 300 mg/codeine phosphate 30 mg to a non-opiate alternative.

Rifampin and Clopidogrel

Clopidogrel is an antiplatelet prodrug whose activation is known to be dependent upon the CYP2C19 phenotype of the given individual. For CYP2C19, there are several variant alleles that will dictate the patient's capacity for prodrug activation (metabolism) to the active metabolite. The most common form of the *CYP2C19* gene, *1, is considered the wild-type, or normal allele, and designates extensive (normal) metabolism. Therefore, an individual that is homozygous (*1/*1) would exhibit extensive metabolism of the clopidogrel prodrug into its active form. Loss of enzyme function is observed in the *2, *3, *4, *5, *6, *7, and *8 variant alleles. Of those individuals that possess a *CYP2C19* loss-of-function allele, approximately 90 percent possess the *2 allele, making it the most common variant form. When paired with the wild-type *1 in a heterozygous individual (e.g., *1/*2), the patient will be an intermediate metabolizer of clopidogrel. Homozygous individuals with decreased function alleles (e.g., *2/*2) are considered poor metabolizers. Additionally, there is one known variant allele that is associated with increased metabolic function, the *17 allele. Individuals that are heterozygous (*1/*17) or are homozygous for the *17 allele are considered ultrarapid metabolizers of clopidogrel.[1,6] It is vital that a patient's phenotype is determined prior to clopidogrel therapy, as this will determine the possibility of therapeutic success that the patient may experience. Typically, with antiplatelet therapy for coronary artery stent placement, if a patient is found to be an intermediate or poor metabolizer, other therapies should be considered due to the lack of complete conversion of the prodrug to its active form and the increased risk of adverse cardiovascular events noted in such patients.[11]

JM is a 49-year-old man who has enjoyed smoking a pack of cigarettes daily for the past 40 years. He has a maternal family history of hypertension and hyperlipidemia. Recently, JM suffered a myocardial infarction while working at his job as a prison guard. During heart catheterization, a stent was placed in two of JM's coronary arteries. JM was started on clopidogrel 75 mg daily. At the time JM started clopidogrel, a blood sample was sent for *CYP2C19* genotyping. The lab reports JM's genotype to be *CYP2C19*1/*2*, thus illustrating the drug-gene interaction. His physician, not being familiar with the genotyping data, increases the clopidogrel dose to 150 mg daily. Several months later, while attending an annual checkup required for all prison employees, JM received a positive tuberculin skin test result. After additional blood and sputum tests were conducted, it was determined that JM had latent tuberculosis, and was placed on rifampin 600 mg therapy for four months.

Rifampin is a known inducer of the CYP2C19 enzyme, and consequently causes a twentyfold increase in the metabolizing capabilities of this enzyme.[6] Therefore, when rifampin and clopidogrel are used concomitantly, the amount of prodrug that is converted to the active metabolite within the body vastly increases for the duration of the dual medication usage. Although JM's genotype remains *CYP2C19*1/*2*, thus reflecting an intermediate metabolizer, his phenotype may now more closely resemble that of a *1/*1 extensive metabolizer. With the increased dose of clopidogrel 150 mg daily being employed, and the increased metabolism of clopidogrel to its active form, higher concentrations of therapeutic metabolite will be found in JM's body. This puts JM at an increased risk of adverse drug events, including bleeding. In reality, as JM is inherently a *1/*2, intermediate metabolizer, he should receive an alternative antiplatelet drug. In this scenario, however, the physician chose to increase the dose of clopidogrel. The addition of rifampin to treat JM completes the drug-drug-gene interaction and the likely phenoconversion of JM from an intermediate to extensive metabolizer, albeit, during rifampin therapy.

Rifampin and Warfarin

The previous example addresses a DDGI relative to a prodrug. The following example addresses a DDGI relative to an active drug, here, warfarin.

NF, a 62-year-old African American male, is admitted to the hospital with chest pain and shortness of breath. He had a positive purified protein derivative (PPD) tuberculin skin test two months ago and, after a chest x-ray, was diagnosed with latent tuberculosis (TB); he currently takes rifampin 600 mg daily. Another chest x-ray shows that his TB had not become active, and the doctor orders a ventilation perfusion scan, which shows that the blood flow in NF's lung is low compared to the air in his lungs. The doctor suspects NF has a pulmonary embolism (PE) and orders fondaparinux sodium injections in order to treat the PE. NF is started on warfarin concomitantly with the intent of using warfarin for anticoagulation therapy beyond the hospital stay. The electronic medical record system allows access to NF's genetic testing results to be retrieved from a secure database. The data indicate that NF has a *CYP2C9*2/*3* genotype, and has the common genotype of vitamin K epoxide reductase complex subunit 1 (*VKORC1*), which is also involved in the response to warfarin. Utilizing the package label pharmacogenomic-based dosing chart, NF is started on 3 mg of warfarin daily.[4,10]

Rifampin is a moderate inducer of the CYP2C9 metabolizing enzyme and thus causes a 50 to 80 percent decrease in the AUC for drugs metabolized by CYP2C9, such as warfarin.[6] The induction of CYP2C9 increases warfarin metabolism, increasing its clearance and shortening the warfarin half-life. This can result in decreased anticoagulation effect putting the individual at risk of clot formation; sub-therapeutic warfarin concentrations can result in clot formation that can have fatal consequences for the patient. Based solely on his genotype of *CYP2C9*2/*3* resulting in a poor metabolizer-like phenotype, the daily warfarin dose of 3 mg would be considered appropriate. However, NF has latent TB and is taking rifampin. The use of rifampin has resulted in a phenoconversion in NF as it has caused an increase in the metabolism of warfarin, resulting in a clearance similar to that of an individual with a *CYP2C9*1/*1* genotype, or that of a normal metabolizer. The 3 mg dose of warfarin would probably not be sufficient in preventing blood clots in a normal metabolizer and is thus not sufficient for NF while the rifampin is increasing his metabolism of warfarin. The dose of warfarin must be guided by monitoring his INR and working to get the value into the therapeutic range.

The pharmacist in the hospital realizes that there is a drug-drug-gene interaction when verifying the warfarin order and calls the doctor in order to prevent NF from being readmitted to the hospital in the future with another blood clot. Warfarin could still be given to NF, but he would require a higher dose (5-7 mg) in order for it to be effective.[4] NF's INR is monitored during his hospital stay, and the warfarin dose increased until his INR is at a therapeutic level.

When NF finishes his course of rifampin therapy in two months, the higher dose of warfarin given previously will no longer be required. Warfarin metabolism will no longer be induced, as the rifampin will no longer be "on board." NF's warfarin dose needs to be decreased because his genotype suggests decreased metabolism as compared to a *1/*1 normal metabolizer. On the current dose and with relatively decreased metabolism, the concentration of warfarin will increase, putting NF at an increased risk for bleeding as noted by a likely supratherapeutic INR.[4] NF's INR should be closely monitored while the dose is being decreased in order to ensure he receives the correct dose.

Conclusion - What this Means for Pharmacists

The above examples depict some of the more distinct cases of phenoconversion that are already evident in practice today. They included both those which led to an increase in function of metabolic proteins and a decrease in function of metabolic proteins, but both were based on allelic differences in genetic make-up relative to concomitant drug use, or a DDGI. Therefore, phenoconversion should be considered within clinical judgment in cases of multi-drug therapy, and knowledge of drug-drug *and* drug-gene interactions is necessary to optimize therapeutic effects while minimizing or avoiding adverse drug events.

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Trametinib and Dabrafenib:
New Agents for Advanced Stage Melanoma

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Abstract

Melanoma, the deadliest form of skin cancer, is caused primarily by exposure to ultraviolet radiation. Tumor formation occurs early in disease progression and can easily metastasize. The development of the disease can be described by one of four stages, characterized by tumor size and risk of spreading. The B-raf protein plays an important role in cell proliferation and has the ability to develop a mutation for continuous activation, resulting in uncontrolled cell growth. Sixty percent of melanomas possess a V600E mutation in the BRAF gene. Recently, drug developers have turned the focus of melanoma treatments toward preventing the activation of the mitogen-activated protein kinase (MAPK) pathway and, consequently, cell proliferation is decreased and leads to cell cycle arrest. Two of the newest U.S. Food and Drug Administration (FDA)-approved medications for the treatment of melanoma are trametinib (Mekinist®) and dabrafenib (Taflinar®). It is important for pharmacists to understand the benefits, side effects and potential warnings involved with trametinib and dabrafenib so they are better able to educate their patients on these innovations in melanoma treatment.

Introduction

Melanoma causes the greatest fatality rates among skin diseases, even though it is not as prevalent as other skin cancers.[1,2] Approximately 76,000 individuals in the United States were predicted to be newly diagnosed with melanoma in 2013, and about 48,000 deaths occur each year worldwide.[3,4] Melanoma is caused primarily by environmental factors, such as ultraviolet radiation from the sun or tanning beds, but the risk of developing melanoma can also be increased by genetic mutations, as will be discussed. Exposure to ultraviolet light may damage deoxyribonucleic acid (DNA) of skin cells, especially melanocytes, leading to mutations resulting in uncontrolled cell growth and tumor formation. This is potentially fatal for patients, especially if cancer cells metastasize to other areas of the body.

Identifying early signs of melanoma is a major step to halt the spreading and prevent the progression of cancer into irreversible stages. According to the American Cancer Society, a mnemonic device of ABCDE is employed to identify warning signs in skin growths or moles in both clinical practice and home examinations. "A" stands for asymmetry of the mole, "B" for borders due to the jagged edges, "C" for color and any changes in color within one area, "D" for diameter of greater than six millimeters (mm) and "E" for evolution of the mole's shape or change in appearance. If detected early in disease progression, the suspected growths of cancerous melanocytes can be surgically removed via biopsy without complications.[5]

The guide used for staging melanoma is classified by Breslow's thickness, defined as thickness of the tumor and its depth of penetration into the skin. Although many sub-stages have been identified, a simplified guide consists of four stages characterized by tumor size with an additional "stage 0" defining an in situ, non-invasive small tumor on the skin surface. Stage I features invasive tumors less than one mm thick. Stage II tumors are between one and two mm thick, may be considered invasive, and generally feature local ulcerations allowing for greater risk of metastasis. Stages III and IV possess tumors with sizes between two mm to four mm and greater than four mm, respectively, but tumor size in these stages is less relevant due to the potential complications of metastasis. According to the American Cancer Society, five year survival rates of stages I and II are between 50 and 90 percent, stage III ranges from 40 to 78 percent and late-stage, stage IV a mere 15 to 20 percent rate.[5] Skin biopsies are no longer sufficient in the spreading stages and adjuvant therapy with anticancer drugs is required.

Current Melanoma Drug Therapy

There are few medications that have been approved and used for treatment of late-stage melanoma. Prior to 2006, the only FDA-approved drug for use in melanoma was dacarbazine (DTIC®), a DNA-alkylating prodrug. It shares many similarities with temozolomide (Temodar®), which is commonly used for late-stage metastatic melanoma. However, temozolomide is only indicated for treatment of two specific astrocytoma-induced brain tumors and is not FDA-approved for melanoma. In 2011, two new drugs gained approval for melanoma, ipilimumab (Yervoy®) and vemurafenib (Zelboraf®). Ipilimumab, a monoclonal antibody, acts by preventing the inhibition of cytotoxic T-lymphocytes thus allowing them to identify and destroy the rapidly dividing cancerous melanocytes. Mutations in the B-raf protein have been associated with tumor development, specifically melanomas that are driven by point mutations in the BRAF gene known as V600E and V600K, which occur in 60 percent and 10 percent of melanomas, respectively.[6] Vemurafenib specifically inhibits the kinase activity of V600E and V600K forms of B-raf, with little activity against the wild-type form. While highly effective, this drug is only useful if the patient has one of the above mutations. To understand the beneficial effects of vemurafenib, an appreciation of B-raf in melanoma is required.[7]

In non-malignant cells, B-raf is a key player in the mitogen-activated protein kinase (MAPK) pathway as shown in Figure 1. Typically, following activation of a membrane-located tyrosine kinase receptor or G protein-coupled receptor, second messenger molecules are generated and intracellular signal-

ing proteins are activated. In several cell types, these events lead to activation of B-raf. B-raf, a serine/threonine kinase, activates mitogen-activated extracellular kinase (MEK) that in turn stimulates extracellular signal-regulated kinase (ERK). Signaling via this pathway leads to activation of gene transcription resulting in several functional effects including increased cell proliferation and survival. Conversely, mutated B-raf (e.g. BRAF V600E) will signal in an unregulated fashion leading to constant activation of the MAPK pathway. Cancerous melanocytes may develop due to this dysregulated signaling and inability of the cell to respond to feedback inhibition that ultimately leads to increased cell proliferation and survival.[8]

New Melanoma Drug Therapy
The development of selective B-raf inhibitors for the treatment of malignancies caused by V600E and V600K mutations represents the first successful application of targeted therapy in melanoma. A clinical challenge with the available B-raf inhibitors is that cancerous melanocytes are able to develop cross-resistance to selective B-raf inhibition through a mechanism whereby the cell switches the isoform of the Raf kinase protein employed for proliferation. Trametinib (Mekinist®) and dabrafenib (Tafinlar®) are recently developed inhibitors of the MAPK pathway and are alternative therapies that may decrease the likelihood of resistance de-

veloping to B-raf inhibition therapy. Specifically, dabrafenib is the most recently introduced B-raf inhibitor, while trametinib is a MEK inhibitor.[9] Although trametinib and dabrafenib are not the first inhibitors of this pathway on the market, both drugs are easier for patients to self-manage and are available in once (dabrafenib) and twice (trametinib) daily oral dosing. The cost of these drugs is also relatively lower compared to a $13,021 30-day supply of vemurafenib. Trametinib and dabrafenib monthly costs summate to $10,440 and $9,120 respectively, significantly lower than that of vemurafenib.[10,11] It has also been shown that exclusive therapy with dabrafenib reduces the absolute risk of squamous cell carcinoma by 22 percent compared to vemurafenib, and shrinkage of tumors was also found in nine of 10 patients.[12,13] Squamous cell carcinoma risk was found to be non-existent in a phase II trial of trametinib. It is evident these two new entities show increased benefits compared to previous MAPK pathway inhibitors.[9]

Dabrafenib
Dabrafenib (Tafinlar®) was approved by the FDA on May 29, 2013, as a treatment for patients with BRAF V600E mutations in unresectable or metastatic melanoma. However, it is not indicated for patients with wild-type B-raf melanoma because of a potential increase in tumor formation.[14] Dabrafenib selectively inhibits the BRAF V600E mutation which, as

Figure 1. Schematic Representation of B-raf and MEK Signaling in Melanoma.[8]
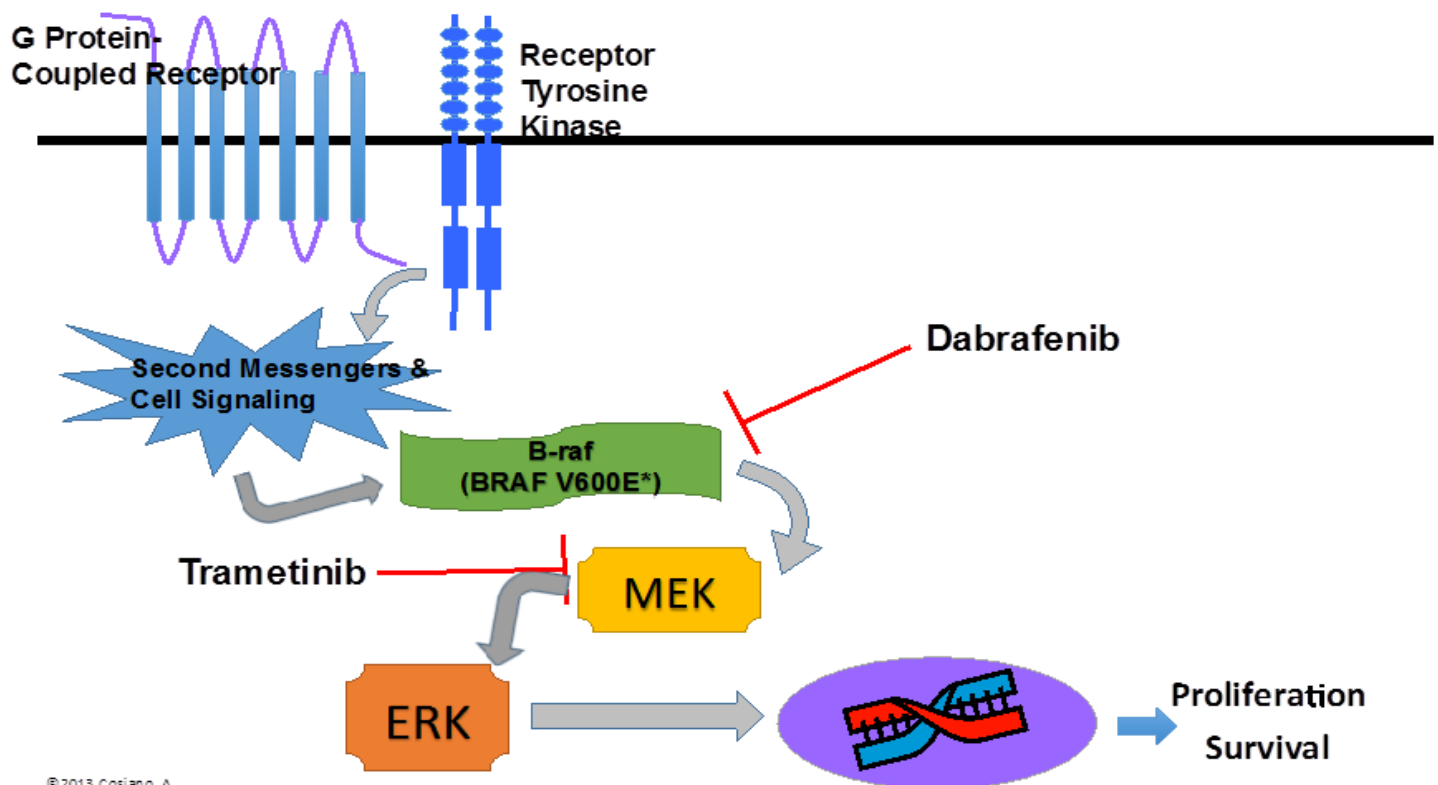
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Certain proteins have been omitted for simplicity in identifying drug targets. Please see text for abbreviations and details of signaling cascade and functional responses. BRAF V600E represents B-raf in which valine at position 600 has been mutated to glutamic acid with a resulting constitutive signaling activity. BRAF V600E may drive the melanoma phenotype and is the specific target of dabrafenib. MEK is activated downstream of B-RAF V600E and stimulates ERK. Trametinib is an inhibitor of the kinase activity of MEK.

described previously, is responsible for constitutive activity of the MAPK pathway and initiating uncontrolled cell proliferation. Blockade of this pathway results in inhibition of tumor cell growth and discontinuation of cancer progression.[11]

Dabrafenib is administered orally, twice daily, in 150 mg doses until disease progression or undesirable toxicity occurs. Recommended dose adjustments for toxicity include: first dose reduction of 100 mg twice daily, second dose reduction of 75 mg twice daily, and third dose reduction of 50 mg twice daily. If the patient is unable to tolerate 50 mg twice daily, dabrafenib should be discontinued. Doses should be taken at least one hour before, or two hours after, a meal. Missed doses may be administered up to six hours prior to the next dose. If less than six hours remain until the next scheduled dose, do not administer.[11]

It is important that the patient is made aware of possible adverse effects prior to the initiation of treatment with dabrafenib. The most common adverse reactions (≥ 20 percent incidence) are hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome.[14] Labeled warnings that should be discussed with the patient are febrile drug reactions, such as fever, chills, and dehydration. Dabrafenib is categorized as a pregnancy risk factor D drug. Females who are pregnant or may become pregnant should not take dabrafenib. Adverse effects were observed in animal studies, and based on the mechanism of action, fetal harm can be expected if dabrafenib is administered to pregnant women due to a potential decrease in the serum concentration of estrogens and progestins. Females with high reproductive potential throughout the course of therapy and four weeks beyond the termination of therapy should use non-hormonal contraceptives. Breast-feeding is not recommended during dabrafenib therapy. Impaired spermatogenesis may also be experienced in males. No dosing adjustments are necessary for mild to moderate renal impairment or mild hepatic impairment. Severe renal impairment and moderate to severe hepatic impairment effects have not been studied. There are no special geriatric considerations for this drug and there is no pediatric dosing information listed. There are also no listed contraindications of dabrafenib with other medications.[11]

The decision for the approval of dabrafenib was based on improved progression-free survival (PFS) by treatment with dabrafenib over chemotherapy, as demonstrated in a randomized (3:1) active-controlled trial. The trial enrolled 250 patients with previously untreated stage III or stage IV melanoma with the BRAF V600E mutation. Participants were randomized to receive either oral dabrafenib 150 mg twice daily (n=187) or dacarbazine 1000 mg/m^2 intravenously once every three weeks (n=63). Sixty percent of the participants were males and the median age was 52 years. A statistically significant PFS was observed in patients receiving dabrafenib therapy (hazard ratio [HR] 0.33, 95 percent confidence interval [CI]: 0.20, 0.54; p<0.0001). The median PFS rates were 5.1 months and 2.7 months in treatment with dabrafenib and dacarbazine, respectively. These data suggest that prolongation of PFS can be obtained by using dabrafenib as a metas-

tatic melanoma treatment.[14]

Trametinib

On May 29, 2013, the FDA approved trametinib (Mekinist®) for the treatment of cancer patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.[13] Trametinib selectively and reversibly inhibits MEK 1 and MEK 2 kinase activity. As described previously, MEK is the subsequent effector of B-raf in the cell proliferation pathway. By inhibiting the activation of MEK 1 and MEK 2, trametinib decreases cellular proliferation, promotes cell cycle arrest, and increases apoptosis of tumor cells.[10] The recommended dose for trametinib is 2 mg once daily by oral route until disease progression or toxicity is identified. If cardiac toxicity, including 10 percent decrease in left ventricular ejection fraction (LVEF) from baseline occurs, it is suggested to interrupt therapy for up to four weeks, then, if LVEF improves to normal, decrease the dose by 0.5 mg. If there is greater than a 20 percent decrease in LVEF, or symptomatic heart failure occurs, discontinue trametinib permanently. If a grade 2 dermatologic rash develops, decrease the dose by 0.5 mg; but if only taking 1 mg daily, discontinue use. If the grade 2 rash does not improve within three weeks of decreasing the dose, or a grade 3 or grade 4 rash develops, interrupt therapy for up to three weeks. If improvement still does not occur after three weeks, discontinue therapy. If grade 2 or 3 retinal pigment epithelial detachments (RPED) occur, interrupt therapy up to three weeks. If RPED improves after three weeks, resume therapy by decreasing the dose by 0.5 mg. If RPED does not improve, discontinue use. Trametinib should be administered at least one hour before, or two hours after, a meal. Missed doses should not be taken within 12 hours of the next dose.[10]

As trametinib is a new treatment option, it is important to educate patients on the possible adverse side effects of the medication when initiating treatment. The most common side effects (≥ 20 percent incidence) include rash, diarrhea and lymphedema.[15] There are no listed contraindications for trametinib with other drugs. Dosage adjustments are not necessary in cases of mild to moderate renal impairment or mild hepatic impairment. Adjustments for severe renal impairment and moderate to severe hepatic impairment have not been defined. Possible adverse events include cardiomyopathy, dermatologic toxicity, ocular complications such as RPED or retinal vein occlusion and pulmonary toxicity. Trametinib is categorized as a pregnancy risk factor D drug. Women who are pregnant or trying to conceive should not take trametinib. No clinical studies have been conducted on pregnant women, but based on the mechanism of action it can be inferred that the medication could cause fetal harm as well as impair fertility. There are no special geriatric considerations to keep in mind, and no information is listed for pediatric dosing considerations.[10]

Recent studies have demonstrated positive responses to trametinib in the treatment of melanoma. The decision to approve trametinib as a melanoma therapy was based on results of increased PFS when compared to chemotherapy.[15] In a phase III randomized active-controlled trial conducted

by Flaherty et al., 322 patients with mutation positive metastatic melanoma were assigned to receive either trametinib or chemotherapy in a 2:1 ratio. Patients in the experimental group (n=214) received trametinib 2 mg once daily, and the patients in the chemotherapy group (n=108) received intravenous dacarbazine (1000 mg/m^2) or paclitaxel (175 mg/m^2) every three weeks. Treatment continued until disease progression was observed, death, or withdrawal from the study. Patients in the chemotherapy group that experienced disease progression were allowed to change therapies to trametinib. The median PFS with trametinib was 4.8 months and 1.5 months with chemotherapy ([HR] for disease progression/death in trametinib cohort, 0.45; 95 percent [CI], 0.33 to 0.63; p<0.001). The overall survival rate at six months was 81 percent with trametinib and 67 percent with chemotherapy.[9]

In addition to the study conducted by Flaherty et al. that investigated the benefits of choosing trametinib over traditional chemotherapy, other trials have been conducted to further specify the population for which trametinib should be indicated. In 2012, Kim et al. published a phase II clinical trial studying the effects of trametinib in patients with metastatic BRAF-mutant cutaneous melanoma that had been previously treated with or without a BRAF inhibitor.[16] Participants were divided into two groups. Participants in cohort A were previously treated with a BRAF inhibitor, while those in cohort B had received chemotherapy and/or immunotherapy treatment prior to the study. Both groups were administered oral daily doses of trametinib 2 mg. Results of the study indicated that the median PFS in cohort A was 1.8 months, whereas the PFS in cohort B was four months.[16] These results confirm that trametinib had a better clinical impact on patients without previous treatment with BRAF inhibitors than those who had received BRAF inhibition treatment. These data suggest that BRAF inhibitor resistance mechanisms may also have an effect on MEK inhibition therapy, and therefore it should be noted that trametinib is not indicated for use in patients who have received prior treatment with BRAF inhibitors.[15]

Conclusion

Since detecting melanoma in its early stages is key to increasing duration and quality of life in patients, the pharmacist needs to have the ability to recognize possible skin irregularities on patients and be able to refer them to their primary care physician or dermatologist. Pharmacists must also be able to provide basic counseling information for trametinib and dabrafenib because these drugs may cause severe side effects, especially when taken incorrectly. Pharmacies may see trametinib and dabrafenib on their shelves relatively soon due to the prevalence of melanoma in the population and the availability of these drugs as an oral dosage form.

Melanoma is a severe type of skin cancer due to its high mortality rates in the metastatic stages of the cancer. Fortunately, two drugs, trametinib and dabrafenib, have recently been approved by the FDA to combat metastatic melanoma and improve the length and quality of life in patients. These newly approved medications are effective due to their selec-

tivity in targeting cells that contain a certain mutation in the BRAF gene. More studies need to be done on genetic expression of melanoma cancer cells in order to increase the chance of finding more mutations or pathways to target with drugs. Furthermore, studies need to further evaluate dabrafenib and trametinib in order to establish more confidence of the safety and efficacy of these medications.

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