Volume 23, Number 6

Shands at the University of Florida

June 2009

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 19, 2009. No drugs were added in the *Formulary* while 1 was deleted. 9 drugs or dosage forms were designated nonformulary and not available. Criteria were changed for 6 drugs, including 2 exceptions to "contraindications."

◆ ADDED

None

◆ DELETED

Lomustine (CeeNu® Dosepack)*

**Nonformulary and must be ordered on Chemotherapy Order Form*

◆ NONFORMULARY AND NOT AVAILABLE

Darifenacin
(Enablex® by Novartis)†

Fesoterodine (Toviaz® by Pfizer)†

Flavoxate (Generic)†

Oxybutynin ER
(Ditropan® XL by Ortho)†

Oxybutynin Transdermal
(Oxytrol® by WatsonPharma)‡

‡Prescriber must change to tolterodine ER or oxybutynin IR

Solifenacin
(Vesicare® by GlaxoSmithKline)†

Tolterodine IR (Detrol® by Pfizer)†

Trospium IR/ER
(Sanctura®/XR by Allergan)†

†Interchanged to tolterodine ER

◆ INTERCHANGES

Tolterodine ER (Detrol® LA) **for Darifenacin** (Enablex®)

Tolterodine ER (Detrol® LA) **for Fesoterodine** (Toviaz®)

Tolterodine ER (Detrol® LA) **for Flavoxate** (Generic)

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MEDICATION SAFETY

Prochlorperazine — the forgotten antiemetic

Data from 2006 attributed 3.7% of Emergency Department (ED) visits to nausea and vomiting, which was the 4th most common reason for an ED visit. Nausea and/or vomiting are the result of peripheral or central stimulation of the chemoreceptor trigger zone (CTZ). Precipitating factors include ingestion of medications or toxins, infection, gastrointestinal obstruction, gastroparesis, pregnancy, migraines, and surgical procedures. Treatment options are usually described as 2 broad categories: antiemetics and prokinetics. Antiemetics include phenothiazines, antihistamines, anticholinergics, dopamine antagonists, and 5-HT_3 antagonists. Prokinetic agents used for dysmotility syndromes include metoclopramide and erythromycin.

Phenothiazines, specifically prochlorperazine and promethazine, are often overlooked with the presence of newer, more heavily promoted antiemetic agents like 5-HT_3 antagonists (eg, ondansetron). However, these agents should not be disregarded. The 5-HT_3 antagonists are used mainly for prevention of nausea. Clinical experience suggests that 5-HT_3 antagonists are not as effective once a patient is vomiting.

Promethazine was developed in the 1930s, followed by prochlorperazine in the 1950s. Initially developed for anesthesia and antipsychotic use, these agents were later found to have antiemetic effects. Over time, antiemetic use became their principal place in therapy. Not only are phenothiazines effective, there are multiple dosage forms available, from oral formulations to suppositories and parenteral routes.

Prochlorperazine has labeled indications for the control of severe nausea and vomiting as well as treatment of schizophrenia. Promethazine is labeled for the treatment of active motion sickness, prevention of postoperative nausea and vomiting, allergic reactions, and to reduce narcotic requirement in some surgical situations.

Although phenothiazines like prochlorperazine and promethazine are in the same general pharmacologic class, they do not have identical primary mechanism of actions or adverse events. Prochlorperazine blocks postsynaptic mesolimbic dopaminergic D_1- and D_2- receptors, which includes the CTZ, explaining its antiemetic effect. Prochlorperazine also has moderate anticholinergic and alpha-adrenergic receptor-blocking activity. Promethazine is primarily a competitive histamine$_1$-receptor blocker with muscarinic M_1-receptor-blocking activity resulting in antihistaminic, sedative, anti-motion-sickness, antiemetic, and anticholinergic properties.

Despite proven efficacy, these medications are not without risks. As recent as March 2009, promethazine was the center of a US Supreme Court decision about product liability. In 2000, a musician went to the emergency room for a migraine with nausea. She received meperidine and promethazine intravenously (IV). At the site of infusion, she developed gangrene that required amputation of the forearm.[1] Intravenous preparations of promethazine have a pH between 4 and 5.5. At this pH, the surrounding tissue can become severely damaged if extravasation from the IV site occurs. We have previously cautioned about this potential problem in the *Bulletin*. Also, cautionary alerts warning nurses to dilute the vial into

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Formulary update, from page 1

◆ **INTERCHANGES (cont.)**

Tolterodine ER (Detrol® LA) **for Oxybutynin ER** (Ditropan® XL)

Tolterodine ER (Detrol® LA) **for Solifenacin** (Vesicare®)

Tolterodine ER (Detrol® LA) **for Tolterodine IR** (Detrol®)

Tolterodine ER (Detrol® LA) **for Trospium ER** (Sanctura® XR)

Tolterodine ER (Detrol® LA) **for Trospium IR** (Sanctura®)

◆ **CRITERIA-FOR-USE CHANGES**

Desmopressin Injection (DDAVP [Generic])§

§Use for uremic bleeding permitted

Dofetilide (Tikosyn® by Pfizer)¶

¶Dofetilide Order Form required

Everolimus
(Afinitor® by Novartis)**

***Chemotherapy Order Form required*

Heparin, Unfractionated
(Generic)††

††Saline used to flush central catheters

Linezolid (Zyvox® by Pfizer)‡‡

‡‡Use with sympathomimetics permitted in monitored units; Progress Note required for use with antidepressants

Oseltamivir
(Tamiflu® by Roche)§§

§§Restricted to ID physician approval

Lomustine is an oral alkylating agent marketed since 1976 that is used to treat Hodgkin's disease and brain tumors. The CeeNU® Dose-Pack, which contained 10-, 40-, and 100-mg capsules, is no longer available. Only the individual capsule strengths are available.

Lomustine has not been used at Shands at UF for several years. Therefore, it was deleted from the *Formulary*. If ordered nonformulary, it still must be ordered on a *Chemotherapy Order Form*.

Darifenacin, fesoterodine, flavoxate, oxybutynin extended-release (ER), **oxybutynin transdermal, solifenacin, tolterodine immediate-release** (IR), and **trospium IR/ER** are antimuscarinic drugs used for symptoms of overactive bladder syndrome (OAB). These agents were designated nonformulary and not available and will be interchanged to an equivalent dosage of tolterodine ER based on the table *(see top of next column)*.

THERAPEUTIC INTERCHANGE OF OAB AGENTS

Interchanged to Tolterodine ER 2 mg daily

Tolterodine IR 1 mg twice a day	Oxybutynin ER 5 mg daily
Darifenacin 7.5 mg daily	Solifenacin 5 mg daily
Trospium IR 20 mg daily	Flavoxate 100 mg 3-4 times/day

Interchanged to Tolterodine ER 4 mg daily

Tolterodine IR 2 mg twice a day	Oxybutynin ER 10-30 mg daily
Darifenacin 15 mg daily	Solifenacin 10 mg daily
Trospium IR 20 mg twice a day	Trospium ER 60 mg daily
Flavoxate 200 mg 3-4 times/day	Fesoterodine 4-8 mg daily

OAB may affect quality of life for some patients and is characterized by symptoms of frequency and urgency, with or without urge incontinence. Antimuscarinic agents are first-line pharmacological options for OAB. There are 6 marketed antimuscarinic drugs with labeled indications for the treatment of OAB. Flavoxate is used off-label for OAB.

There is no consensus on the preferred agent for the treatment of OAB. Oxybutynin IR tablets and syrup and tolterodine ER capsules have been listed in the *Formulary*. Over the past year, there has been little use of the other agents in this class.

The comparative efficacy and safety of the various antimuscarinic agents used for OAB have been evaluated in systematic reviews and meta-analyses. The most recent and comprehensive of these reviews show no significant difference in efficacy among the antimuscarinic agents for OAB. ER products may be preferred over IR products in patients who experience adverse reactions (ADRs). In clinical trials, patients treated with tolterodine ER rarely discontinued therapy because of ADRs.

Detrol® LA is the most commonly prescribed drug used to treat OAB. It is the 66th most common prescription in community pharmacies (ie, 5.6 million prescriptions). Tolterodine ER was selected to represent OAB drugs so that the fewest number of interchanges will be necessary.

Oxybutynin IR tablet and syrup remain in the *Formulary* for patients taking it as a home medication and for patients unable to take oral solid dosage forms.

Desmopressin is a synthetic analog of the endogenous hormone arginine vasopressin, which is often referred to as DDAVP. DDAVP® is a brand name, but it is also an acronym for 1-**d**eamino-8-**d**-arginine **v**aso**p**ressin. Natural vasopressin is also called antidiuretic hormone (ADH), which is secreted by the hypothalamus in response to various physiologic stimuli. For example, hyperosmolality and volume depletion stimulates ADH release, which causes the normal kidney to reabsorb water from the renal tubules and adjusts serum osmolality and fluid balance. During severe hemorrhage, large quantities of ADH are secreted for its pressor effect. Like many endogenous hormones, ADH has various other physiologic effects, including the stimulation of clotting factors (ie, factor VIII and von Willebrand factor [vWF]).

DDAVP has labeled indications for diabetes insipidus, enuresis, and bleeding in patients with hemophilia or von Willebrand's disease. It is used off-label for various uses including uremic bleeding. Patients with advanced kidney disease are predisposed to bleeding because of platelet dysfunction. DDAVP improves platelet function, presumably because it stimulates vWF.

According to the official labeling, DDAVP use is contraindicated in patients with a creatinine clearance less than 50 mL/min. The clearance of DDAVP is reduced, which may cause an unexpected degree of water accumulation leading to hyponatremia. However, there are instances in which it may be appropriate to use DDAVP in patients with kidney disease.

Uremic bleeding typically presents with ecchymoses, purpura, epistaxis, and bleeding from venipuncture sites. These patients can also present with gastrointestinal or intracranial bleeding. Because DDAVP normalizes bleeding time in 75% of patients with chronic renal failure, it is the most common agent used in active uremic bleeding. DDAVP doses for uremic bleeding are approximately 10-fold higher than doses used for diabetes insipidus (0.3 mcg/kg to 0.4 mcg/kg IV or SQ as a single injection). An important advantage of DDAVP is its rapid onset of action for acute bleeding caused by uremic platelet dysfunction.

Studies have shown that DDAVP decreases bleeding time within an hour after injection. Alternative options (eg, cryoprecipitate; erythropoietin) take hours to weeks to show effects. DDAVP has a short duration of activity; bleeding time returns to baseline within 24 hours. Disadvantages of DDAVP include reported tachyphylaxis after 1 dose, headache, facial flushing, and rare thrombotic events.

Despite the labeled contraindication, the P&T Committee determined that DDAVP is a reasonable option to treat uremic bleeding, even though these patients have a creatinine clearance less than 50 mL/minute.

(continued on next page)

Formulary update, *from page 2*

Dofetilide is a class III antiarrhythmic used for the conversion and maintenance of normal sinus rhythm in patients with atrial fibrillation/flutter. Because of its risks, it is reserved for highly symptomatic patients.

Drugs that inhibit dofetilide metabolism or renal elimination may increase the risk of dofetilide-induced proarrhythmias. In addition, concomitant use of dofetilide with drugs associated with QT prolongation or torsade de pointes is contraindicated. To minimize the risk of induced arrhythmia, patients initiated or re-initiated on dofetilide must stay a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic (ECG) monitoring, and cardiac resuscitation. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education.

Because of these limitations, errors of omission upon admission to the hospital must be considered. It may be unacceptable to stop dofetilide during a patient's admission (for a non-cardiac reason) to avoid these interactions and possible risks. Do not stop dofetilide without consulting the patient's cardiologist.

In order to use dofetilide, patients must be followed by a cardiologist registered in the restricted-distribution program. Therefore, the dofetilide policy was revised to include a pre-printed *Dofetilide Order Form* for patients continuing home therapy on non-cardiology services. This order set contains an automatic order for a Cardiology Consult to ensure appropriate management of patients who may otherwise not be monitored. The patient's chart must include an order for this service.

Everolimus is a kinase inhibitor with a labeled indication for the treatment of advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. Neither sunitinib (Stutent®), nor sorafenib (Nexavar®) are listed in the *Formulary*. Everolimus is pharmacologically different from sunitinib or sorafenib because it inhibits a specific kinase inhibitor, mammalian target of rapamycin (mTOR).

Everolimus was not added in the *Formulary*, but it was added in the *Chemotherapy Policy*. If prescribed for an inpatient, the order must be written on a *Chemotherapy Order Form*.

Unfractionated heparin and saline are used to maintain the patency of (ie, "flush") intravenous catheters. The Nursing Department's Clinical and Evidenced-Based Council requested that the P&T Committee endorse a change from heparin to saline for the flushing of temporary central venous catheters in adult patients. This recommendation is based on insufficient evidence to support the use of heparin and risks associated with heparin use (ie, risk of heparin-induced thrombocytopenia [HIT] and inadvertent heparin systemic anticoagulation [including possible overdoses]).

Recent benchmarking showed that many institutions use saline to flush central venous lines (CVLs). Manufacturer information for the central venous catheters used at Shands at UF recommends the use of saline or "local practice" and cites the Intravenous Nursing Society (INS) standards. Therefore, the P&T Committee endorsed the use of saline instead of heparinized saline to maintain the patency of temporary central venous catheters in adults.

Linezolid is a unique antibiotic used primarily to treat resistant enterococcal infections and methicillin-resistant *Staphylococcus aureus* (MRSA) infections in patients that are either intolerant or refractory to vancomycin therapy. Use of this agent has increased as the number of resistant gram-positive infections has increased. Linezolid is a "last-line" antibiotic for resistant gram-positive infections.

The concomitant use of linezolid and selective serotonin reuptake inhibitors (SSRIs) or sympathomimetic agents are frequent contraindicated drug-drug interaction alerts generated by the pharmacy's computer system. According to the product labeling, linezolid is contraindicated in patients taking SSRIs, tricyclic antidepressants, triptans, meperidine, or buspirone (unless carefully observed for signs and/or symptoms of serotonin syndrome). Linezolid is also contraindicated in patients taking directly and indirectly acting sympathomimetic agents (eg, pseudoephedrine), vasopressive agents, or dopaminergic agents (unless monitored for potential increases in blood pressure).

A P&T Committee-authorized *Linezolid Progress Note* was approved, which will be placed in a patient's chart when they are on linezolid and an antidepressant. The progress note reminds the prescribers of the "contraindicated" combination and provides a list of options (monitor for signs/symptoms of serotonin syndrome; consider an alternative antibiotic; or discontinue the antidepressant).

It may not be possible to discontinue either of the interacting agents (eg, linezolid or SSRI) safely. The progress note will serve as a reminder to prescribers to keep serotonin syndrome in their differential diagnosis when treating patients' symptoms. Even if the SSRI is stopped, drug persists in the body and a reaction may be possible.

Since the interaction with pressors results in an elevated blood pressure and patients will be monitored in critical care settings, this is an exception to the contraindication. Thus, linezolid and pressors can be used together in monitored units.

Pseudoephedrine should always be stopped when a patient is on linezolid. Midodrine, which is used to treat hypotension, may be used with linezolid, since the purpose of midodrine is to increase blood pressure and patients are monitored.

Oseltamivir is a neuraminidase inhibitor with a labeled indication for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year of age and older who have been symptomatic for no more than 2 days. Because of its activity against type A influenza viruses, it is a drug of choice for the treatment of the current H1N1 virus that is causing swine-originated influenza (or the "swine flu").

Effective May 8, 2009, the P&T restricted the use of oseltamivir to patients that have been approved for inpatient use by an infectious diseases physician. This action was recommended by the Resistant Pathogen Task Force near the beginning of the swine flu outbreak. The goal is to ration supplies so that drug is available for the neediest patients (see table below).

These criteria are not absolute, and ID physicians will use their discretion at determining "high risk." When this restriction will end will be determined by whether the swine flu epidemic persists throughout the summer months.

CRITERIA FOR OSELTAMIVIR USE IN HOSPITALIZED PATIENTS [ONLY]

- Patients with a confirmed case of swine-originated influenza virus (S-OIV)
- Patients with a probable case of S-OIV
- Acute febrile respiratory illness who is *Influenza A* positive
- Patients with a suspected case of S-OIV
- Acute febrile respiratory illness within 7 days of close contact with a confirmed or probable case of S-OIV
- Acute febrile respiratory illness within 7 days of travel where there are 1 or more confirmed cases of S-OIV
- Patients with acute febrile respiratory illness **and** who are at high risk of complications
- Immunocompromised patients
- Pregnant females
- Patients < 5 yrs or > 65 yrs of age
- Patients with chronic respiratory and cardiopulmonary conditions

"Cockcroft-Gault for drug dosing... not MDRD"

There has been a debate about whether the Modified Diet in Renal Disease (MDRD) method of estimating glomerular filtration rate (eGFR) or the Cockcroft-Gault (C-G) method of estimating creatinine clearance (CrCl) should be used to guide drug dosing in patients with impaired renal function. A recent study showed that the MDRD method of estimating renal function could result in subtherapeutic drug dosing in patients with stage IV or V kidney disease and supratherapeutic drug dosing in patients with stage III disease (assuming the C-G method provides the "correct" dosage).[1]

Both C-G and MDRD are estimates of renal function. A creatinine clearance may need to be measured when patients have characteristics that make the C-G unreliable. For example, the C-G equation *(see box below)* relies on the patient's serum creatinine value to estimate creatinine clearance. When a patient's creatinine production is atypical (patients with liver disease, patients who are cachectic), the C-G equation may overestimate a patient's renal function. A patient may receive too much drug based on an overestimate of their creatinine clearance. Regardless of the method of estimating creatinine clearance, it may be necessary to measure the patient's renal function or drug levels when the risk of an overdose is high.

The National Kidney Disease Education Program (NKDEP) does not recommend the use of MDRD for drug dosing in patients with renal impairment.

COCKCROFT-GAULT EQUATION*†‡

Estimated Creatinine Clearance (mL/min) =
[140 – Age (yr) x weight (Kg)] ÷ [72 x Serum Creatinine (SCr)]

*Multiply by 0.85 for females

†Use Ideal Body Weight (kg) = men = 50 kg + (2.3 kg x inches greater than 5 ft); women = 45.5 kg + (2.3 kg x inches greater than 5 ft)

‡Normalize for BSA (1.73 m2)

The National Kidney Disease Education Program (NKDEP) does not recommend the use of MDRD for drug dosing in patients with renal impairment.[2] Current dosing recommendations were based on the C-G method of adjusting dosing. Therefore, the P&T Committee endorsed the NKDEP position on using Cockcroft-Gault versus MDRD for drug dosing in patients in impaired renal function.

MDRD remains the preferred method of estimating a patient's renal function and identifying patients with kidney disease. Shands already complies with the NKDEP recommendation that laboratory creatinine values be standardized with calibration traceable to isotope dilution mass spectrometry (IDMS).

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MEDICATION SAFETY

Ceftriaxone-calcium update

Ceftriaxone is an injectable third-generation cephalosporin with activity against gram-positive and gram-negative bacteria. Its penetration into the central nervous system has made it a valuable agent in the treatment of meningitis. Its long half-life allows for once-daily dosing.

In December 2007, the criteria for ceftriaxone use at Shands at UF were reviewed based on changes to the product's labeling, which included a contraindication for the co-administration of ceftriaxone and calcium-containing intravenous solutions, including parenteral nutrient preparations, in neonates age 28 days or younger. Ceftriaxone was already contraindicated in hyperbilirubinemic newborn infants.

Warnings were added in the labeling stating that ceftriaxone should not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines, and that calcium-containing solutions or products must not be administered within 48 hours of the last administration of ceftriaxone. These warning were based on 5 neonatal deaths reported between 1992 and 2002 by post-marketing surveillance where there was an association between ceftriaxone and calcium-containing products and crystalline material found in the kidney and lungs upon autopsy.

On April 14, 2009, the FDA modified ceftriaxone's labeling, and the labeling is now consistent with the restrictions approved by the Shands P&T Committee in 2007.

In 2007, the P&T Committee found no conclusive evidence to support a significant safety risk of ceftriaxone in non-neonates; therefore, ceftriaxone use in children 28 days old or younger was prohibited based on the contraindication language in the labeling. Use in children older than 28 days old and adults was not restricted.

On April 14, 2009, the FDA once again modified ceftriaxone's labeling, and the labeling is now consistent with the restrictions approved by the Shands P&T Committee in 2007.[1] The contraindication in children less than or equal to 28 days of age with intravenous calcium containing products remains. Patients older than 28 days old may receive these products sequentially provided the infusion lines are flushed thoroughly. The FDA no longer considers administration of calcium-containing products and ceftriaxone contraindicated for 48 hours of the last dose of ceftriaxone. These changes were based on 2 in vitro studies using neonatal and adult plasma. Ceftriaxone still should not be mixed with calcium in the same IV or by Y-site administration, regardless of the patient's age.

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Drugs & Therapy
B · U · L · L · E · T · I · N

Volume 23, No. 6 June 2009
This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

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Medication safety, *from page 1*
a volume of 10 mL of normal saline before administration of IV promethazine have been added to dispensing cabinets. Some hospitals have considered totally removing promethazine from their formularies.

Many institutions stopped using prochlorperazine and switched to promethazine during a prochlorperazine shortage in 2001 (which has since resolved). Unfortunately, an increase in adverse events was associated with the change.[2] The promethazine product labeling states that the preferred route of parenteral administration is a deep IM injection; however, IV is frequently used. The IM route is preferred to the IV because promethazine is a known vesicant. If administered intra-arterially, promethazine can cause gangrene, as in the previous case, and subcutaneous administration may cause tissue necrosis. Other injuries reported include burning, erythema, severe spasm of vessels, thrombophlebitis, venous thrombosis, phlebitis, nerve damage, paralysis, abscess, and tenderness at the injection site. Prochlorperazine infusion has less severe infusion-related reactions but is associated with hypotension and akathisia if administered as a bolus.

In addition to warnings about administration, promethazine has a black-box warning contraindicating its use in children less than 2 years of age and advising caution to be used in children 2 years and above due to a potential risk for fatal respiratory depression. Prochlorperazine carries a similar contraindication to its use in children 2 years of age or younger or less than 20 pounds. Both promethazine and prochlorperazine also carry a risk of hypotension; therefore, the lowest effective dose and caution should be used in patients with cardiovascular issues. Long-term use or high doses of any phenothiazine may result in akathisia and extrapyramidal symptoms.

The Institution of Safe Medical Practices (ISMP) includes promethazine IV in its list of high-alert medications and has recommended multiple strategies to prevent or reduce tissue damage when promethazine is administered IV. Some of these practice recommendations are to limit the dose, use a large patent vein, and educate the patients to alert the provider immediately of any burning or pain with the infusion. Prochlorperazine does not carry these warnings, although there is evidence that administration as an IV infusion, rather than as a bolus, has a lower incidence of akathisia.

These phenothiazines are not often compared, but a randomized, double-blind clinical trial comparing time to relief for IV prochlorperazine and IV promethazine in uncomplicated nausea and vomiting found prochlorperazine was superior at 30 and 60 minutes. Additionally, the prochlorperazine group had fewer treatment failures and complaints of drowsiness. There was no difference in the frequency of akathisia between the 2 groups.[4]

Providers have many options for the treatment of nausea and vomiting. Prochlorperazine should be considered as an early option for nausea and vomiting since it has established efficacy and it can be given by multiple routes of administration. When IV administration is necessary, prochlorperazine has the advantage of having limited, relatively minor infusion-related reactions. Suggested equivalent parenteral (IV/IM) doses of prochlorperazine for promethazine are 5 to 10 mg of prochlorperazine for 6.25-12.5 mg and 25-50 mg of promethazine, respectively. This can be repeated every 3 to 4 hours with a maximum daily dose of 40 mg.

By Julia Logan, PharmD

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