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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met September 19, 2006. 3 drugs or dosage forms were added in the *Formulary*, and 2 were deleted and designated nonformulary and not available. There were 5 criteria-for-use changes and 2 automatic dosage interchanges approved.

◆ ADDED

Levetiracetam Injection (Keppra® Injection by UCB Pharma)

Nitazoxanide (Alinia® by Romark Laboratories)*

**Restricted to the Inpatient GI Medicine (MGI) Service or Approval by ID, Antibiotic Management Program, or a Clinical Pharmacist.*

Rifaximin (Xifaxan® by Salix Pharmaceuticals)

◆ DELETED

Spectinomycin (Trobicin® by Pfizer)†

†*Nonformulary and Not Available (no longer marketed)*

Vancomycin Capsules (Vancocin® by ViroPharma)‡

‡*Nonformulary and not available (oral liquid will be used instead)*

◆ CRITERIA-FOR-USE CHANGES

Buprenorphine Sublingual Tablets (Subutex®)**

***Restricted to patients treated for opioid maintenance upon admission.*

Drotrecogin (Xigris®)††

††*New adult order form with more stringent criteria for use.*

Fondaparinux (Arixtra®)‡‡

‡‡*No longer requires Hematology Approval.*

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POLICIES AND PROCEDURES

Standard insulin infusions: The L&D Exception

For more than 6 months, the standard intravenous insulin infusion concentration has been 0.5 units per mL of normal saline. This concentration was selected to make titrating dosages more precise, and, for the most part, this has been very successful.

Like all attempts to standardize, there are situations where exceptions need to be considered. In the Labor and Delivery (L&D) Post-Anesthesia Care Unit (PACU) and the Mother-Baby Unit, it has been the standard of care for post-Cesarean-section patients requiring insulin to be managed with a very low concentration of insulin in dextrose 5%. The 0.5-unit-per-mL standard in normal saline could not be used to deliver the typical dosage of 1 unit of insulin per hour.

Standard OB-GYN textbooks were used to justify an exception to the standard insulin concentration for use in post-C-Section patients in the L&D PACU and Mother-Baby Unit. In this specific population, a 0.01 unit per mL in dextrose 5% will be the standard. These "nonstandard" bags will be labeled to draw attention to its unique concentration and base solution.

PRESCRIBING

Make up your mind: Acetylcholine or no acetylcholine

A patient is admitted with a chief complaint of confusion and disorientation. After a thorough workup, it is determined that the patient has Alzheimer's disease. The service would like to start a medication to slow further progression; however, she is taking amitriptyline 50 mg at bedtime and Detrol LA® (tolterodine) 4 mg daily. Fortunately, an important drug interaction was identified that is often overlooked.

Alzheimer's disease is common in the elderly, affecting approximately 10% of those over the age of 65 and nearly half of those over 85. Typically, cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, are the treatments of choice for mild to moderate Alzheimer's disease. These medications act by selectively inhibiting acetylcholinesterase, which improves the availability of acetylcholine in the synaptic cleft. Unfortunately, these medications are relatively expensive and only mildly effective in treating the cognitive deficits associated with Alzheimer's dementia.

The potential for drug interactions increases exponentially in the elderly due to the number of medications they often take. Approximately 35% of patients receiving cholinesterase inhibitors are simultaneously receiving at least 1 potent anticholinergic agent. It has been suggested that anticholinergic medications diminish potential benefits from cholinesterase inhibitors and may exacerbate the cognitive decline in Alzheimer's disease. This is the interaction identified in the patient that introduced this article.

A retrospective study examined chronic exposure to anticholinergic medications in a small cohort of Alzheimer's dementia patients and demonstrated a significant decline in mental status at 2 years.[1] Mental status scores were significantly worse

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Formulary update, *from page 1*

◆ CRITERIA-FOR-USE CHANGES (cont.)

Vancomycin Liquid (compounded from injection)[***]

[***]*Restricted: Requires approval by ID, the Antibiotic Management Program, or approval by a clinical pharmacist.*

◆ AUTOMATIC DOSAGE CHANGES

Drotrecogin (Xigris®)[†††]

[†††]*Automatic dose rounding down to the nearest vial size approved.*

Magnesium Intermittent IV Replacement Infusions (compounded)[‡‡‡]

[‡‡‡]*Adults must use 2-, 4-, or 6-gram "boluses"*

Levetiracetam injection was added in the *Formulary* as a line-item extension for oral levetiracetam. Levetiracetam is an antiepileptic with a labeled indication as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. The injectable dosage form is used when oral administration is temporarily not feasible. There is little evidence to support off-labeled uses at this time; thus, the off-labeled use of levetiracetam injection will be monitored.

Nitazoxanide is the first in a new class of anti-infectives known as the thiazolides. It is a broad-spectrum agent with demonstrated *in vitro* activity against a wide variety of pathogens including protozoa, helminthes, anaerobic bacteria, and viruses. However, nitazoxanide only has labeled indications for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum* in patients 1 year of age and older.

There are limited data for off-labeled use of nitazoxanide for the treatment of diarrhea secondary to other intestinal pathogens including *Clostridium difficile*-associated diarrhea (CDAD) and Rotavirus; *Helicobacter pylori* dyspepsia; and, intestinal helminthes, nematodes, and cestodes. Current data do not show superiority of nitazoxanide over metronidazole in the management of CDAD. However, clinical data suggest nitazoxanide may play a role in patients who have previously failed repeated doses of metronidazole or oral vancomycin treatment.

Nitazoxanide was added in the *Formulary* but restricted to the Inpatient GI Medicine (MGI) Service or approval by Infectious Diseases, the Antibiotic Management Program, or a clinical pharmacist. Nitazoxanide will be used for the management of diarrhea secondary to *Cryptosporidium parvum* and as a second-line agent for the management of *Clostridium difficile*-associated diarrhea in patients either intolerant to metronidazole or deemed a clinical failure to repeated courses of metronidazole therapy.

There are not enough data at this time to support the use of nitazoxanide for treatment of chronic hepatitis. There are limited data to support the use of nitazoxanide in the treatment of patients with Crohn's disease, but it may be an reasonable option in patients who have developed neurotoxicity to metronidazole. This recommendation is based on its antimicrobial activity and not demonstrated efficacy in clinical trials.

Nitazoxanide appears to be well-tolerated. Common adverse reactions are mild and transient, with gastrointestinal discomfort being most commonly reported.

Nitazoxanide is nearly 80 times more expensive than metronidazole. It costs more than $25 per day. Whenever possible, oral metronidazole, which costs $0.32 per day, should be used.

Rifaximin, a semi-synthetic derivative of rifamycin, is useful in the management of gastrointestinal infections due to its low bioavailability. It has a labeled indication for uncomplicated traveler's diarrhea, but it is frequently used off-label for the treatment of hepatic encephalopathy and *Clostridium difficile*-associated diarrhea (CDAD).

Clinical trials indicate that rifaximin may also be an alternative to current therapy for treatment of hepatic encephalopathy. Studies show that rifaximin is as efficacious as lactulose or neomycin and confirm that rifaximin is well-tolerated. Although the risk for nephrotoxicity is extremely rare with oral neomycin, rifaximin may be an alternative in patients with severe renal dysfunction.

There is a theoretical concern about resistance with gram-positive bacteria and cross-resistance with other rifamycins. Therefore, prudent use of rifaximin is recommended. Most adverse events associated with rifaximin are gastrointestinal in nature.

Rifaximin was added in the *Formulary* as either a second- or third-line agent for the treatment of hepatic encephalopathy. In patients with acute or chronic renal insufficiency, rifaximin may be an option in patients that have received an adequate trial of lactulose. In patients without renal insufficiency or those with end stage renal disease with no possibility of renal function recovery, it is a third-line agent only after the patient has received an adequate trial of lactulose, neomycin, and/or a combination of both.

Clinical evidence is lacking to support the use of rifaximin in the treatment of CDAD and; therefore, it should not be used for this indication.

Rifaximin is roughly 5 times more expensive than lactulose and 3 times more expensive than neomycin. There will be ongoing monitoring of the use of rifaximin to determine whether restrictions on its use are needed.

Vancomycin capsules were deleted from the *Formulary* and deemed nonformulary and not available. **Oral vancomycin liquid** made from the injection will be the only oral form of vancomycin available. The use of oral vancomycin liquid will be restricted to *Clostridium difficile*-associated diarrhea approved by Infectious Diseases, the Anti-Infective Management Program, or a clinical pharmacist.

Oral vancomycin was reviewed when nitazoxanide and rifaximin were evaluated as possible alternatives for *Clostridium difficile*-associated diarrhea. Oral vancomycin use for the treatment of CDAD has been associated with the development of vancomycin-resistant enterococci (VRE). Thus, limiting it use was deemed necessary.

Spectinomycin is no longer being marketed due to low sales volume and, therefore, will be deleted from the *Formulary*.

Spectinomycin is an antibiotic that has been on the market since 1971. Historically it has been used for the treatment of acute gonorrheal urethritis in males and acute gonorrheal cervicitis and proctitis in females. Third-generation cephalosporins or fluoroquinolones have now replaced spectinomycin as the antibiotics of choice for the management of these infections. A primary use of spectinomycin has been the treatment of gonorrhea in pregnant women who have a history of hypersensitivity reactions to penicillins. OB-GYN physicians are now using a very high dose of azithromycin (2 grams) in this situation.

The Shands at UF criteria for **buprenorphine sublingual tablets** were expanded to include continued treatment of patients admitted for the treatment of a medical problem. In January 2006, buprenorphine tablets were added in the *Formulary,* but were restricted to use at Shands Vista by physicians registered to prescribe it for opioid detoxification, opioid maintenance, and for use in chronic pain in patients with a history of opioid dependence. Subutex® was also deemed "not available" at Shands at UF.

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Formulary update, *from page 2*
However, there have been a few patients transferred to Shands at UF from Shands Vista with medical problems who were receiving Subutex® for the previous indications. This was problematic at Shands at UF because patients cannot use their own supply of controlled substances. (Subutex® is a Schedule III controlled substance.)

Thus, for these rare instances, the criteria for use for Subutex® have been changed to allow continuation of their opioid maintenance therapy. Although information from the Drug Enforcement Agency (DEA) and the Substance Abuse and Mental Health Services Administration (SAMHSA) conflicted, a FAQ on the SAMHSA website states, "a patient with opioid addiction who is admitted to a hospital for a primary medical problem other than opioid addiction…may be administered opioid-agonist medications (eg, methadone, buprenorphine) in this circumstance." The FAQ further recommends that the admitting physician consult with the patient's addiction treatment provider to obtain a treatment history.

The mandatory order form for **drotrecogin** has been updated and includes new limitations on its use. Drotrecogin is recombinant protein C used to prevent the complications of severe sepsis in patients at a high risk of death. The revised order form now specifies that it is for adults only. A pediatric form is being developed.

The revised form has additional check boxes (eg, inclusion and exclusion criteria), additional demographic information collected (eg, patients actual body weight), several technical wording changes, and additional information on compatibility data. However, the main criteria-for-use change is the requirement that there be 3 out of 4 criteria for systemic inflammatory response syndrome (SIRS) and 2 organ failures before using drotrecogin. This limits use to more severely ill patients and matches current literature recommendations.

The revised form requires the calculation of the patient's APACHE II score and that drotrecogin be given only to patients with scores greater than 25. Data show that there is no demonstrated benefit for drotrecogin in patients with low APACHE II scores and that there is the potential risk of adverse effects.

This form allows for rounding doses down to the nearest vial size if the dose is changed less than 10%. Because increasing the dose of drotrecogin has potential safety issues, rounding doses up to the nearest vial size is considered too risky.

Fondaparinux is a synthetic anticoagulant used to prevent and treat thromboembolic disorders. When it was added in the *Formulary* in November 2005, it was restricted to approval by the Hematology Service. This restriction has been lifted.

Fondaparinux has labeled indications for the prevention of deep venous thrombosis/pulmonary embolism (DVT/PE) in orthopedic surgeries (hip and knee replacements and repair of hip fractures) and in abdominal surgery patients. It also has labeled indications for the treatment of DVT and PE.

There will now be standardized **magnesium intermittent IV replacement bags** that will be used for parenteral magnesium supplementation. In order to promote medication safety, intravenous magnesium replacement bags (sometimes inappropriately referred to as magnesium "boluses") will be standardized. By limiting the number of intravenous magnesium doses, it enables the purchasing of commercially available pre-made bags in doses at the appropriate dilutions. Standardization of IV doses decreases the chances of incorrect dosages and compounding errors.

All adult intravenous magnesium replacement doses will be automatically changed to 2 grams, 4 grams, and 6 grams based on the following: 2 grams will be dispensed for any order less than 3 grams; 4 grams will be dispensed for orders greater than or equal to 3 grams, but less than 5 grams; and, 6 grams will be dispensed for any dose greater than or equal to 5 grams. No single doses greater than 6 grams will be allowed. If larger doses are needed, a separate dose can be ordered. All dosage changes will be documented in the Orders and Progress Notes sections of the chart as with all other interchanges.

POLICIES AND PROCEDURES

No samples allowed…

There are currently no areas in the hospital that can dispense samples. Hospital policy allows the use of samples for outpatients in areas under the control of the hospital only when that area can comply with regulations on the storage, labeling, and dispensing. Samples can never be used for inpatients, staff members, or family members. The complete policy along with all the requirements that must be followed to use samples can be found on the Shands intranet at http://intranet.shands.org/pharm/pdf/03-16.pdf.

Vouchers, which allow patients to obtain a starter supply of medication from any pharmacy, are a recommended alternative to samples in the hospital setting. Vouchers do not have the rigorous requirements that must be legally followed to use sample medications.

Prescribing, *from page 1*
for patients receiving anticholinergic medications than for those who were not.

Medications from several therapeutic classes have varying degrees of anticholinergic properties and are listed in Table 1 *(see page 4)*. These agents can contribute to clinically significant mental status changes that range from mild cognitive impairment to delirium. The Beers criteria, a guideline for safe medication use in the elderly, recommend that some of these medications be avoided in the elderly regardless of mental state.[2] This recommendation, in addition to the interaction with cholinesterase inhibitors, make it especially necessary to avoid the use of anticholinergic agents in patients with dementia.

A study conducted by Carnahan and colleagues evaluated concomitant use of anticholinergic medications and cholinesterase inhibitors.[3] This study evaluated the use of anticholinergics upon inception of treatment with a cholinesterase inhibitor and found that ranitidine was the most common anticholinergic medication administered while concurrently on a cholinesterase inhibitor, followed by oxybutinin, amitriptyline, and tolterodine. The study also showed that the rate of concomitant use did not change after inception of the cholinesterase inhibitor, suggesting that prescribers do not account for patients' dementia by discontinuing the anticholinergic medications.

Several approaches may be taken to avoid this drug interaction. Physicians may choose to discontinue the anticholinergic medication, discontinue pharmacologic therapy for Alzheimer's disease, or substitute another agent in place of the cholinesterase inhibitor. The simplest way to avoid this interaction is to discontinue the anticholinergic agent. For example, amitriptyline and Detrol LA® in the case could be replaced by alternative therapies. It is important that sleep hygiene be assessed before addition of a medication to treat insomnia. If a medication is necessary, trazodone or zolpidem may be appropriate alternatives to amitriptyline. If the patient requires an anticholinergic due

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Prescribing, from page 3
to urinary incontinence, first consider nonpharmacologic approaches, such as limiting fluid intake and Kegel exercises, which are often more effective than pharmacologic therapy. Anticholinergics are often prescribed to counteract the adverse effects of the cholinesterase inhibitors, such as gastrointestinal upset and urinary incontinence. If a patient cannot tolerate these adverse effects, a dose reduction should be considered. It may even be necessary to discontinue the cholinesterase inhibitor, which may be a better option than adding an anticholinergic medication. Treating an adverse effect with another medication is never optimal, especially when potentially eliminating the therapeutic effects of the cognitive enhancer.

Memantine may be used as a therapeutic alternative for cholinesterase inhibitors. Memantine is an N-methyl-D-aspartate receptor antagonist that is effective alone or in combination with donepezil for the treatment of Alzheimer's disease. Due to the distinct mechanism of action, memantine may be a better choice for patients that require anticholinergic agents.

It is important to frequently assess the medication profiles of geriatric patients and make all efforts to avoid the use of anticholinergic medications concomitantly with cholinesterase inhibitors. Ideally the rate of concomitant use would be zero; however, there may occasionally be a situation where the combination is considered clinically appropriate. In general, medications with anticholinergic properties should be used with caution in geriatric patients, especially when they are currently on a cholinesterase inhibitor.

By Marlena Fox, PharmD

TABLE 1: ANTICHOLINERGIC PROPERTIES OF DRUGS

THERAPEUTIC CLASS	MEDICATIONS	ANTICHOLINERGIC ACTIVITY
Tricyclic Antidepressants	Amitriptyline, doxepin, nortriptyline	High
Urinary Incontinence Agents	Oxybutinin, tolterodine	High
Antiarrhythmics	Disopyramide	High
Antispasmodic Agents	Dicyclomine, hysoscyamine	High
Antihistamines	Cimetidine, diphenhydramine, hydroxyzine, promethazine, ranitidine	Low
Skeletal Muscle Relaxants	Carisoprodol, cyclobenzaprine, methocarbamol	Low

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