

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 21, 2012. 7 products were added in the *Formulary*, 1 product was designated a high-priority nonformulary drug, and no drugs were deleted from the *Formulary*. 2 products were designated nonformulary and not available. 1 criterion for use change was approved.

◆ ADDED

AbobotulinumtoxinA (Dysport®)*

*Restricted: Florida Surgical Center Movement Disorders Clinic Only

Arginine Base Powder, USP (Generic)

Azelastine Nasal Spray (Generic)

Darunavir Oral Suspension (Prezista®)

IncobotulinumtoxinA (Xeomin®)*

Lisdexamfetamine (Vyvanse®)

Raltegravir Chewable Tablet (Isentress®)

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

Fentanyl Sublingual Spray (Subsys®)†

Olopatadine Nasal Spray (Patanase®)†

†Patients MAY use their own supply from home

◆ HIGH PRIORITY NONFORMULARY DRUG

Carnoy's Solution, Modified (Compounded)†

†Obtained from a compounding pharmacy on a patient-specific basis

◆ INTERCHANGES

None

(continued on next page)

PRESCRIBING

Opioid Prescribing in “Naive” or “Tolerant” Patients

Opioids are frequently associated with medication errors and can result in serious consequences. Underdosing can result in inadequate pain control and poor patient care. Overdosing can result in patient harm. Keeping patients' pain adequately controlled requires selecting the appropriate drug and appropriate dosage. Good care includes appropriate assessment of effectiveness and monitoring for potential toxicities.

Although opioids are often titrated to the effective dose to avoid dose-dependent adverse effects, the appropriate starting doses or the use of potent and/or long acting dosage forms for chronic pain depend on whether patients are “opioid tolerant” or opioid naïve.

Tolerance implies less than the expected response to an opioid. Tolerance can be a genetic predisposition or acquired. At this point, there is no way to predict genetic traits that would require higher starting doses.

Acquired tolerance is the primary focus of this review. As patients take opioids, they will require higher doses to obtain the desired pain relief. How long does this tolerance take to develop? How much opioid per day is associated with tolerance?

For example, transdermal fentanyl “patches” should only be used in patients who are already receiving opioid therapy and **who have demonstrated tolerance and who are not opioid naïve**. Giving potent, long-acting opioids like a fentanyl patch to opioid naïve patients has resulted in deaths. Thus, fentanyl patches should NOT be used for acute pain.

Opioid tolerance is defined in the fentanyl official labeling as those who take at least 60 mg of oral morphine daily (or an equianalgesic dose of another opioid). This is the **lowest** daily dose of opioid a patient must be receiving in

order to be prescribed the **lowest** dose of fentanyl patches. This is a conservative definition of opioid tolerance. This “FDA endorsed” definition of opioid tolerant is also found in many of the new Risk Evaluation and Mitigation Strategy (REMS) documents and FDA-approved Medication Guides for new opioids.²

Minimum Opioid Tolerant Daily Doses

Codeine Oral – 150 mg per day
Fentanyl Patch – 25 mcg transdermal/day
Hydromorphone Oral – 8 mg per day
Meperidine IM – 75 mg per day
Methadone Oral – 20 mg per day
Methadone IM – 10 mg per day
Morphine Oral – 60 mg per day
Oxycodone Oral – 30 mg per day

Naïve implies that the patient is not already taking opioids. How long does it take before a patient is no longer naïve and is now “tolerant?” In general, tolerance does not develop in days. Opioid naïve implies patients are not chronically receiving opioids on a daily basis. “Opioid tolerant” implies patients are chronically receiving opioids on a daily basis.

Tolerance is associated with chronic pain, not acute pain, although increasing doses can occur with acute pain. Carefully titrating acute doses avoids complications. “As-needed” dosing is usually not associated with tolerance.

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INSIDE THIS ISSUE

◆ Restricted drugs in EPIC

◆ CRITERIA-FOR-USE CHANGES

Palivizumab (Synagis®)*

*Restricted: RSV treatment must be approved by an ID attending AND the director of the Anti-Infective Management Program

AbobotulinumtoxinA and incobotulinumtoxinA were added in the *Formulary* and restricted to the use by physicians of the Movement Disorders Clinic at the Florida Surgical Center (FSC). In November, these botulinum toxin type A products were designated nonformulary and not available. The P&T Committee decided that they could be used safely in this specific setting by qualified physicians. A review by medication safety pharmacists will be done to try to optimize the safety procedures for these products at FSC to avoid any possible confusion among the products.

Botulinum toxins now have generic names that differentiate among the various forms of toxins. Products have different potencies, and the units for these agents are NOT equivalent. Generic names are supposed to prevent medication errors, although brand names are usually used.

Botulinum toxins are used for a variety of uses where the "toxin" paralyzes muscle. Since Botox® has been on the market the longest, it has the most labeled and off labeled uses; however, theoretically, any botulinum toxin could be used for these uses as long as the appropriate dose is used.

In 2009, FDA added a boxed warning to botulinum toxins to emphasize the risks of spread of the toxin beyond the site it is injected. FDA has also mandated a Risk Evaluation and Mitigation Strategy (REMS) to explain that botulinum products cannot be interchanged and explain the risk of toxin spread.

The decision to add these additional toxins were based on concern about the development of antibodies with switching products, although there is no current evidence to document this problem. There are data showing less antibody formation with Xeomin®, which could result in more persistent efficacy over time. This could lead to use in young children with dystonia, who will be administered these products over a long period. However, there is no current evidence linking antibody formation with lack of effect. Switching among the products in the Movement Disorders Clinic could be problematic. This was balanced by concerns about their

safe use and possibility for medication errors, particularly if other physicians use botulinum toxins at FSC. The P&T Committee agreed that switching product was not ideal as long as sufficient safety measures are in place to prevent product confusion.

Arginine Base Powder, USP was added in the *Formulary* for the oral administration of arginine in patients with rare genetic disorders that impair the formation of arginine. These urea-cycle disorders can result in hyperammonemia if not treated with arginine.

The P&T Committee has previously decided to interchange arginine powder orders to an oral liquid arginine made from the injection. Arginine powder was nonformulary and not available because it is usually a dietary supplement, not a drug. Patients who needed oral arginine supplementation were given an equivalent amount of the IV formulation orally. Injectable arginine is the hydrochloride (HCl) salt.

A recent patient with arginine deficiency, who was acidotic lead to questions about this policy because there was concern that the hydrochloride salt could contribute to the patient's acidosis. For this reason, the P&T Committee reconsidered the interchange policy.

Two USP-grade powder formulations of arginine were located, the base and the hydrochloride salt. Since a USP-grade arginine base powder could be purchased by the Pharmacy Department, it was added in the *Formulary*. There was concern about stocking both base and HCl powder formulations, and possible dispensing and administration errors. Therefore, IV arginine HCl will be administered IV only. The base [only] will be given orally.

Azelastine is an intranasal histamine receptor-1 (H₁) antagonist and an inhibitor of mast cell histamine release. It has a labeled indication for the treatment of mild to moderate seasonal and perennial allergic rhinitis. Increasing nonformulary use has been noted by pharmacists.

Data support the therapeutic equivalency of azelastine to oral H₁ antagonists and intranasal corticosteroids as measured after weeks to months in clinical trials. However, data are not available to describe the magnitude and rapidity of azelastine's effect over shorter periods likely to apply to inpatients. Patients that are well controlled on azelastine nasal spray may be reluctant to switch to an oral antihistamine. Therefore, azelastine nasal spray was listed in the *Formulary*.

Olopatadine nasal spray was designated nonformulary and not available, but patients may use their own supply from home.

Darunavir oral suspension and raltegravir chewable tablets will be added in the *Formulary* as soon as they become commercially available, which is consistent with the philosophy of

making new drugs and dosage forms used for the treatment of HIV infections readily available. Since non-compliance can lead to resistance, a delay in therapy because a drug is not readily available could contribute to treatment failures.

Darunavir is an antiretroviral protease inhibitor used in the treatment of HIV. Recommended adult dosages range from 800 mg daily to 600 mg twice daily boosted with 100 mg ritonavir. Reduced dosages are recommended for children and adolescents. Children greater than or equal to 15 kg should be assessed for their ability to swallow tablets. If a child is unable to swallow a tablet, darunavir suspension is an option. Children should be given darunavir suspension twice a day with food. Complete dosage recommendations and dose rounding recommendations are available in the official labeling.

Raltegravir is an integrase inhibitor used as an antiretroviral agent for the treatment of HIV. The labeled daily dose is 400 mg twice daily in adults and children 6-11 years old weighing greater than or equal to 25 kilograms. Safety and efficacy of raltegravir were not established previously for children less than 6 years old or those 6-11 years old weighing less than 25 kg. The FDA approved a chewable tablet formulation of raltegravir that is available in 25-mg and 100-mg strengths to aid lower dosages in pediatric patients. The labeling now gives dosage recommendations to children as young as 2 years old.

The 400-mg, film-coated tablets are not bioequivalent with the 25-mg or 10-mg chewable tablets, and the manufacturer states that these products cannot be interchanged. The official labeling states the film-coated tablet should not be crushed, cut, or chewed.

Lisdexamfetamine is a prodrug of dextroamphetamine, a centrally acting stimulant indicated for use in Attention-Deficit Hyperactivity Disorder (ADHD). It is a Schedule II controlled substance, but is formulated with d-amphetamine covalently bonded to L-lysine, which is designed to have less potential than other amphetamines for abuse, diversion, or toxicity.

Many pediatric patients have been admitted taking lisdexamfetamine, which has been nonformulary and not available. Furthermore, patients were not permitted to take their own supply per Shands policy that prohibits the use of a patient's own supply of scheduled drugs. Despite this policy, some parents have tried to administer lisdexamfetamine to their children against the advice of nurses and pharmacists.

(continued on next page)

Formulary Update, from page 2

Additional concerns include defiant behavior in children, which may be aggravated in children whose ADHD medication is discontinued. There is also no exact dosing equivalency conversion to other stimulants used in ADHD.

Lisdexamfetamine has expected adverse effects similar to other stimulants (*ie, decreased appetite, nausea, vomiting, slowing of growth, weight loss, dry mouth, irritability, and insomnia*). Exacerbation of motor and phonic tics, seizures, aggressive behavior, and cardiac affects (*increased blood pressure*) may also occur.

There is no evidence that lisdexamfetamine offers a therapeutic advantage over any other formulation of amphetamine in children for ADHD, but it was added to facilitate continued therapy from the outpatient setting.

Subsys[®] is another **sublingual** dosage form [**spray**] of the potent opioid **fentanyl**. It was approved with a labeled indication for the management of breakthrough pain in opioid-tolerant adult cancer patients. It is only available through a restricted distribution system (TIRF REMS), which requires patients, pharmacies, and distributors to be enrolled. Like other “non-conventional” fentanyl dosage forms, Subsys[®] was designated nonformulary and not available. Since it is a Schedule II controlled substance, patients may not use their own supply from home.

Carnoy's solution is a compounded solution that was first used as a tissue fixative agent (*ie, stabilizing agent for ex-vivo human tissue*) in the 19th century but started to be applied as a cauterizing agent for the treatment of odontogenic keratocysts (OKCs) in the late 20th century. Carnoy's solution serves as an adjunct to surgical removal of OKCs, promoting chemical necrosis and elimination of epithelial remnants and microcysts. It is applied for a brief period after surgical removal of a tumor or cyst.

The following formula was recommended by Cutler and Zollinger in 1933, however, “**modified**” formulations eliminate chloroform as it has been found to be carcinogenic: absolute alcohol 6 mL, chloroform 3 mL, glacial acetic acid 1 mL, and ferric chloride 1 gm.

When used appropriately, Carnoy's solution is generally considered safe for the treatment of odontogenic keratocysts (OKCs); however, most studies do not examine adverse events. The true safety profile is unknown. In addition, there are limited data supporting its effectiveness for the treatment of OKCs.

Modified Carnoy's solution's adverse effects include abnormal sensation, hypesthesia, and anesthesia. These adverse effects tend to be mild

and temporary and are similar to those reported in patients receiving other treatments, such as enucleation.

OKCs are aggressive cysts of the jaw and due to their aggressive nature, the World Health Organization (WHO) recently reclassified them as keratocystic odontogenic tumors (KCOT). KCOTs are most commonly located in the mandible and occur most often in males aged 20-40. Recurrence rates have been estimated to be 30% on average but some have reported recurrence rates as high as 62%. Cysts most often recur in the 5 years after treatment.

Most of the data on Modified Carnoy's solution comes from retrospective case series and systematic reviews. These studies estimate the recurrence rate with Modified Carnoy's solution to be 1.6-20%. One small, prospective, randomized study compared enucleation alone and enucleation with Carnoy's solution. This study reported recurrence rates of 11.1% for enucleation alone and 5.6% for Carnoy's solution. The difference was not statistically significant; however, this study was underpowered. One retrospective study showed that Carnoy's solution prevented recurrences statistically better than when it is not used.

Modified Carnoy's solution will be restricted to use as part of a specific protocol that delineates how and when it should be used in order to reduce the risk of adverse effects and promote its safe use. Carnoy's solution is flammable and special precautions will be taken in the operating room.

Since compounding caustic product is difficult because of the corrosive nature of the ingredients and special handling requirements, a small amount will be obtained from a compounding pharmacy on a patient-specific. Since it will not be stocked, it is not listed in the *Formulary*. However, it is considered a high-priority nonformulary drug with procedures established for obtaining product through the Pharmacy Department, when it is needed.

Palivizumab is a composite monoclonal antibody with an FDA-labeled indication for prevention of respiratory syncytial virus (RSV) in pediatric patients at high risk of severe disease. It targets the ‘F’ glycoprotein on the surface of RSV, which is responsible for viral fusion to the cytoplasmic membrane of the host. By targeting this protein, it exhibits neutralizing and fusion-inhibitory activity against RSV. It is given once monthly throughout RSV season (*November through March*) at a dose of 15 mg/kg for prophylaxis.

Palivizumab was added in the *Formulary* in 1998 for RSV prophylaxis in children less than 2 years of age with severe broncho-pulmonary dysplasia who require supplemental oxygen. Since that time, some literature suggests using palivizumab for the treatment of RSV disease. There are cur-

rently no large randomized, controlled trials assessing palivizumab for treatment of RSV. All studies performed to-date have been single center with small sample sizes, mainly focusing on hematopoietic stem cell transplant (HSCT) recipients. Of 11 studies analyzed, only 2 had a primary outcome that concentrated on the effect of palivizumab on clinical outcomes. The remaining studies were phase I studies, descriptive, or assessed the use of a treatment algorithm that included palivizumab, usually for patients with severe disease. Most lacked a comparator group, making it difficult to determine efficacy. In each study, the authors were unable to conclude that palivizumab alone had an effect on clinical outcomes.

Drawing from the limited data available, the use of palivizumab alone or when added to other therapies for the treatment of RSV has not been proven to affect either progression of disease or mortality in a statistically- or clinically-meaningful manner. In addition, the acquisition cost of a dose of palivizumab for a 70-kg patient is over \$23,000.

Until further data are available to determine if palivizumab has any positive effects on clinical outcomes when added to traditional therapy, the P&T Committee restricted its use for RSV treatment. It is not recommended for the treatment of RSV. If ordered for treatment, palivizumab use requires the approval of an Infectious Diseases Attending AND the Director of the Anti-Infective Management Program (*ie, 2 approvals*).

Opioid Tolerant?, from page 1

Chronic pain implies scheduled dosing around the clock. Opioid tolerance is associated with taking opioids routinely for 1 week or longer.

Opioids, opioid doses, and opioid dosage forms that should only be used in opioid tolerant patients should only be used when daily doses exceed those listed in the table on page 1 AND the patient has been receiving chronic therapy for at least a week.

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2. Rappaport BA. Proposed Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS). January 4, 2012. Accessed online March 4, 2012 at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM289730.pdf>.

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POLICIES AND PROCEDURES

Using Epic to Document Criteria for Use

It is so easy; you click a button to order a restricted drug. All you have to do is pick one of the options. The problem is that none of the options fit your patient. The use for the drug you want to prescribe is not listed. You do not want to delay therapy, so you click a listed option so you can prescribe the needed drug.

The problem is you just placed an inaccurate statement in the medical record. This is one example of how the electronic medical records and computerized prescriber order entry (CPOE) have changed things. In the old "paper world," you wrote the order and waited for somebody to tell you whether there were any restrictions or not. If there were restrictions, you might verbally say it was being used for an approved indication...even if it was not. There was no permanent record of what you said.

CPOE provides several mechanisms to enforce P&T Committee approved

restrictions on drugs. One method is to require the prescriber to answer questions that would determine whether the intended use meets the medical staff-approved restriction on its use.

◆

**In the old "paper world,"
you wrote the order and
waited for somebody to tell
you whether there were
any restrictions or not.**

Clicking an option is documenting the justification for use in the "electronic" medical record and provides a basis for pharmacist verification of the order and retrospective reviews for compliance.

Putting inaccurate information in the medical record can have consequences. Florida statutes state that any person who fraudulently alters, defaces, or falsifies any medical record, or causes or procures any of these offenses to be committed, commits a misdemeanor

of the second degree, punishable as provided in Chapter 775.082(4) (6) FS or Chapter 775.083(1)(e) FS. 775.082 and 775.083 set penalties and fines for all similar "crimes." A conviction under subsection (1) is also grounds for restriction, suspension, or termination of license privileges. Not only do practitioners risk losing their license, they risk losing their privileges at a health care facility. Further, inaccurate information in the chart could affect insurance coverage for a patient. If the insurance is Medicare, the consequences could be more serious. So, if you run into a circumstance where you feel you have no choice but to falsify the medical record to order a drug, call the pharmacist in your area to determine whether there are other options. It may avoid patient harm and serious consequences.

REFERENCES

1. 395.302(2) FS.