

Drugs & Therapy

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FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 18, 2003. 4 drugs or dosage forms were added in the *Formulary* and 3 drugs or dosage forms were deleted. Several products were designated not available.

◆ ADDED

Ethinyl estradiol + Norgestrel
(eg, Lo/Ovral® by Wyeth)

Midodrine
(ProAmatine® by Shire)

Pancrelipase (Ultrase® by Axcan Scandipharm)

Treprostinil (Remodulin® by United Therapeutics)

◆ DELETED

Dinoprostone
(Prostin® E2 and Prepidil®)

Pancrelipase (Pancrease® MT by McNeil Pharmaceutical)

Thiothixene (Navane® by Roerig)

◆ NONFORMULARY AND NOT AVAILABLE

Combination Oral Contraceptives*

*except a Lo/Ovral® equivalent

Pancrelipase (all brands, except Ultrase®)**

**Creon® 5 and Viokase® remain available.

Valdecoxib (Bextra® by Pfizer)

A combination oral contraceptive (OC) containing **ethinyl estradiol** 0.03 mg and **norgestrel** 0.3 mg was added in the *Formulary* for use in patients with acute, heavy uterine
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PRESCRIBING

Is once-a-day better than twice-a-day?

How well a medication works (ie, effectiveness) is a function of efficacy and compliance. Efficacy is measured in controlled clinical trials. Compliance is measured in studies that compare patients' actual dosing histories with the prescribed regimen. The best medications do not work if patients do not take them. Medications that are taken reliably work better.

Once-daily medications are often more expensive, but they do simplify a patient's schedule.

There is a large body of literature examining medication compliance.¹⁻⁵ These studies sometimes use different terminology. The terms "adherence" and "persistent" are synonyms for what is commonly referred to as compliance. This research consistently shows that there is an inverse relationship between the number of doses per day and rates of compliance. In other words, the more doses a patient must take per day, the lower their compliance. Whether there is a clinically relevant difference in the compliance rates between once- and twice-daily dosing is debatable, however.

There are more and more drugs that can be given once a day. As drug patents expire, manufacturers often release once-daily versions of medications that previously needed to be given twice or more per day. Once-daily medications are often more expensive, but they do simplify a patient's schedule. Often medications that are given twice a day cost a fraction of the once-daily versions of the medication. If patients cannot

afford the more expensive medications, these may be a good option to consider. If medication costs prohibit patients from getting their prescriptions filled, this obviously hurts compliance—and treatment effectiveness.

What is the difference in compliance between once-daily and twice-daily medications? Studies designed to measure compliance use various techniques. Self-reported compliance, blood-level measuring, prescription refill records, "pill" counts, and electronic monitoring all have been used. Electronic monitoring uses a computer chip in the cap of the prescription bottle and measures each time the bottle is opened. Electronic monitoring is considered the most accurate measurement of compliance.

A systematic review of the association between the number of doses per day and medication compliance that only included studies that used electronic monitoring found that compliance rates were 79% with once-daily dosing and 69% with twice-daily dosing. This difference was not statistically significant. There was considerable variability among the studies. However, this small and statistically insignificant difference in compliance rates is consistent among the studies. Regardless of the method used, there is no detectable difference in the compliance rates between once-daily and twice-daily dosing.

Another aspect to the once-daily versus twice-daily dosing debate must

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bleeding due to anovulatory cycling, ITP, or acute leukemia. These patients receive multiple daily doses (ie, 3 or 4 times a day) of an OC to prevent uterine bleeding. Immediate access to an OC is needed for these circumstances.

Until now, there was no OC listed in the *Formulary*. When a patient did not bring in her own supply and needed to continue taking an OC during her hospitalization, it had to be obtained from Outpatient Pharmacy (if that patient's brand was stocked). This was logistically difficult, especially when the Outpatient Pharmacy was closed.

Now only 1 combination OC will be available. A generic equivalent to Lo/Ovral® was selected because it is commonly used for contraception and can be used in patients at risk for uterine bleeding. All other combination OCs are now nonformulary and not available.

When an order for a nonformulary combination OC is written, the pharmacist will call the nursing floor to determine whether the patient has her own supply. This home medication can be used according to existing policy, which requires a written order specifying the OC and daily dosage.

If a patient does not have her own supply and the prescriber wants to continue an OC during the patient's hospitalization, a generic equivalent of Lo/Ovral® will be recommended. The patient can resume their home OC upon discharge.

Because patients may miss a dose of their OC in the hospital for various reasons (eg, NPO, nausea), the following guidelines can be used when doses are missed. If a patient misses 1 dose, the missed dose should be taken as soon as possible. The next dose should be given at the usual time. This may mean taking 2 tablets on the same day—or even at the same time. Patients can resume their normal dosage schedule and no additional contraceptive is needed.

If a patient misses 2 doses of an OC, she should resume therapy by taking the last missed tablet as soon as possible—again this may mean taking 2 tablets at the same time. She could resume her OC, but should abstain from sex or use an alternate form of contraception for 7 days after resuming therapy.

If 3 or more doses are missed, a patient should begin a new OC-regimen on the first Sunday after discharge. The patient should abstain from intercourse or practice an alternative form of contraception until 7 days after resuming therapy.

Midodrine is an alpha-1 agonist used in the symptomatic treatment of orthostatic hypotension. The FDA approved midodrine in 1996 as a priority drug based on increases in the 1-minute standing systolic blood pressure. Clinical benefits, like improved ability to function, are the goals with this drug; however, standing systolic blood pressure is considered a surrogate marker for this clinical benefit. Midodrine has also been used for intradialytic hypotension.

There are several published studies that show the effectiveness of midodrine in increasing blood pressure in patients with orthostatic hypotension. Patients are hypotensive for a variety of reasons including neurogenic syndromes (eg, Parkinson's disease, diabetic neuropathy, pure autonomic failure, and Shy-Drager syndrome) and intradialytic fluid loss.

Midodrine causes adverse effects expected for an alpha-1 agonist. Marked elevation of blood pressure can occur; therefore, it should be used only in patients who are considerably impaired and who have failed other therapies (eg, support stockings). Urinary retention is a possible adverse effect of this alpha-1 agonist.

Pancrelipase products were reviewed to standardize what is listed in the *Formulary*. There are various brands of pancrelipase products, as well as generics. The Ultrase® MT product line was selected as the only pancrelipase brand that will be available. Ultrase® is less expensive than Creon® or Pancrease®, which were the other brands considered.

Pancrease® MT was deleted from the *Formulary*. Creon 5 was added in the *Formulary* because it is the only pancrelipase dosage that can be administered to small children through the nipple of a bottle. With these exceptions, all other pancrelipase products (besides Ultrase®) will be nonformulary and not available. Ultrase® MT-12 can be used instead of Pancrease® MT-10 or Creon® 10; Ultrase® MT-18 can be used instead of Pancrease® MT-16; and, Ultrase® MT-18 can be used instead of Pancrease® MT-20 and Creon® 20.

Treprostinil is a prostacyclin analogue used to treat pulmonary hypertension. It is an alternative to epoprostenol (Flolan®), bosentan (Tracleer®), and sildenafil (Viagra®). Treprostinil is given by subcutaneous infusion. Thus, it may be useful in some patients who cannot tolerate epoprostenol, which must be given intravenously. Patients who have repeated catheter site infections (eg, children or elderly) might benefit from conversion to treprostinil.

Treprostinil causes vascular smooth muscle relaxation. It is also a potent inhibitor of platelet aggregation. In clinical trials, treprostinil improved walking distance, dyspnea, and pulmonary hemodynamics. The data suggest that treprostinil is a viable alternative in patients who often do not have many options.

It is estimated that the annual cost of treprostinil is \$250 per day (\$96,000 per year), which is approximately 25% more than epoprostenol. Because the pain associated with treprostinil administration makes this drug intolerable to many patients, the use of treprostinil is expected to be minimal.

Patients must be financially qualified by the distributors of treprostinil (Priority Healthcare) in order to continue to receive treprostinil after they are discharged. Since the supplier of treprostinil will also supply the subcutaneous infusion pumps, patients will have to be financially qualified before treprostinil is started at Shands at UF. Priority Healthcare will train nursing staff and patients on the appropriate use of the drug when it is started.

Dinoprostone is prostaglandin E2 that has been used as an oxytocic. It is available as a suppository (Prostin® E2), gel (Prepidil®), and as a removable insert (Cervidil®).

Dinoprostone suppositories and gel were listed in the *Formulary*, but their use for cervical ripening has been supplanted by misoprostol and mechanical means. Since the suppositories and gel are not being used, dinoprostone was deleted from the *Formulary*.

Thiothixene oral concentrate was discontinued by its manufacturer. Upon further evaluation, it was determined that injectable thiothixene is also no longer available. Thiothixene tablets, although listed in the *Formulary*, are not used. Therefore, thiothixene was deleted from the *Formulary*.

Thiothixene is a high-potency "typical" antipsychotic that has been on the US market since 1967. Like other older antipsychotics, the use of thiothixene has decreased because of the potential for long-term adverse effects, like tardive dyskinesia.

Valdecoxib is the newest COX-2 specific nonsteroidal anti-inflammatory drug (NSAID). Pharmacologically, it is the most specific NSAID for the COX-2 receptor of the currently marketed products. Because of insufficient evidence justifying its use and the availability of other therapeutic options, it was designated nonformulary and not available.

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Current evidence-based reviews concluded that there are limited data to support the use of COX-2 inhibitors and no data to support the use of 1 COX-2 inhibitor over another. The evidence comparing celecoxib (Celebrex[®]) and rofecoxib (Vioxx[®]) is inconsistent and inconclusive. There is insufficient evidence available to conclude that there are differences in either efficacy or safety data among the COX-2 inhibitors. Celecoxib is the only COX-2 listed in the *Formulary*.

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be considered. If a patient misses a once-daily dose, they miss an entire day of therapy. If only one dose of a twice-daily dose is missed, they are “partially” treated for that day. One study showed that days without dosing were observed twice as frequently with the once-daily dosing compared with a twice-daily regimen.

There is also the issue of medication “forgiveness” for noncompliance. The forgiveness period is the time that a medication’s effect persists after a dose is missed. If a medication’s duration of effect is more than 12 hours but less than 24 hours, it needs to be given twice a day. The patient will receive a therapeutic effect for more than the 12 hour dosing interval. The forgiveness period equally applies to both once-daily and twice-daily medications.

Patients use cues to remind them when to take their medications (eg, breakfast, dinner, bedtime). When the cues are changed or interrupted,

There is insufficient evidence to show any difference in efficacy between COX-2 selective and nonselective NSAIDs. There is currently insufficient evidence to conclude that COX-2s are preferred over traditional NSAIDs in preventing ulcer complications. Misoprostol and proton-pump inhibitors given with nonspecific NSAIDs decrease the risk of GI complications.

There are data that show that rofecoxib has a statistically significantly lower incidence of gastro-

intestinal events compared with nonspecific NSAIDs. Celecoxib has a lower incidence of GI events compared with traditional NSAIDs when patients are not taking aspirin. Concomitant aspirin eliminates the lower incidence of GI effects with COX-2 inhibitors.

There may be an increased risk of cardiovascular complications with COX-2 inhibitors; however, the data are currently limited. The clinical significance of these findings requires additional research.

are not adequately treated, they consume more resources. More importantly, patients experience morbidity and can even shorten their lives by being noncompliant. Twice-daily regimens are reasonable options, particularly when they are more affordable for patients who have difficulty paying for more expensive once-daily dosage forms.

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PRESCRIBING

Using diuretics in patients with “sulfa” allergies

Sulfonamide allergies are commonly reported. These reactions are usually associated with sulfonamide antibiotics. However, prescribers are often faced with problems caused by the potential for cross-reactivity with other sulfonamide drugs. For example, a patient labeled with a “sulfa” allergy may need a “sulfonamide” diuretic.

Sulfa allergy is a general term used to describe patients with allergies to sulfonamide antibiotics. However, this does not imply allergy to compounds containing sulfur, inorganic sulfate, or sulfites.¹

A sulfonamide is any compound with an SO₂NH₂ group in its structure. Major structural differences exist between sulfonamide antibiotics and other sulfonamide-containing drugs, such as furosemide or thiazide diuretics. This structural difference

allows the division of sulfonamide-containing products into 2 groups: aromatic amines and nonaromatic amines.¹ These chemical differences make the likelihood of cross-reactivity unlikely.

Adverse drug reactions may be categorized into predictable (also known as pharmacological) or unpredictable (or intrinsic) reactions. Predictable reactions result from exaggerated or undesirable pharmacological effects of a drug. These reactions are often dose-dependent. Approximately 80% of all adverse drug reactions (ADRs) are classified as predictable reactions.¹

Unpredictable ADRs are generally independent of dose or pharmacological action of the drug. Examples include idiosyncratic reactions and various immunologic reactions or allergic reactions. Unfortunately, these

terms have been used with varying connotations by patients, health care practitioners, and throughout the literature. Many patients may refer to an ADR from a sulfonamide antibiotic (ie, nausea, vomiting, diarrhea) as an allergy. “Allergy” should only be used to describe reactions to drugs involving the immune system.

“Hypersensitivity reaction” is a general term for both allergic and idiosyncratic reactions. Idiosyncratic reactions can result from the formation of reactive metabolites. These metabolites, if not detoxified, directly bind to cellular and circulating proteins leading to toxicity. Although these reactions are rare, they may affect a number of organ systems. Idiosyncratic reactions do not produce IgE. Therefore, the terms idiosyncratic and allergic are not synonymous.¹

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Sulfonamide ADRs may manifest in a variety of clinical presentations. Some examples of predictable reactions include nausea, vomiting, headache, and other neurological disturbances. Unpredictable reactions include both allergic and idiosyncratic reactions.¹

In true allergic (ie, IgE-mediated) reactions, a chemical group other than the sulfonamide moiety is responsible for triggering IgE antibody production. Structural differences distinguishing sulfonamide antibiotics as aromatic ring structures are responsible for IgE production. Furosemide and thiazide diuretics do not contain these components and are nonaromatic compounds. Although these sulfonamide diuretics may be responsible for a variety of adverse drug reactions, there is little evidence to support cross-reactivity between aromatic sulfonamide antibiotics and nonaromatic sulfonamides.²

The sulfonamide moiety in sulfonamide antibiotics does not trigger serious drug reactions (eg, hypersensitivity reactions). The aromatic amine moiety is critical in the pathogenesis of these reactions, as well as severe cutaneous reactions (eg, Stevens-Johnson syndrome and toxic epidermal necrolysis).³ The nonaromatic amines, such as hydrochlorothiazide,

furosemide, and torsemide, would not be expected to cross-react with sulfonamide antibiotics for these serious drug reactions. However, patients who experience a serious drug reaction with 1 sulfonamide antimicrobial would be expected to have a cross-reaction with all sulfonamide antibiotics.²

An important source of information about the use of a drug is the official product labeling (ie, package insert). Rather than clarifying the confusion that exists regarding cross-reactivity among the various sulfonamide drugs, product labeling actually creates more confusion. There is inconsistent labeling of sulfonamide-containing drugs for use in patients with a history of sulfonamide allergy. For example, hydrochlorothiazide is contraindicated in patients with a sulfonamide allergy, whereas only a precaution is listed in the furosemide labeling.¹

Limited choices exist for diuretics that do not contain sulfonamide structures. Products include 2 potassium-sparing diuretics, amiloride (Midamor[®]) and triamterene (Dyrenium[®]) and 1 loop diuretic, ethacrynic acid (Edecrin[®]). Triamterene is not listed as single-entity product in the *Formulary*. It is available only as a combination product with hydrochlorothiazide.

Ethacrynic acid and amiloride are available as single entities, but they have limited usefulness. They are also associated with significant adverse effects. Ethacrynic acid is a classic agent known to cause ototoxicity. Amiloride and triamterene may cause a more benign hyperkalemia, but their potencies as diuretic agents are low.

A conservative approach in using a diuretic for a patient with a "sulfa allergy" would be to use a structurally unrelated compound. However, a detailed medication history may reveal that a patient is not really allergic to sulfonamides. The benefits compared to risks for each patient must be considered. In some instances, the use of a "sulfonamide-like" diuretic (eg, furosemide) may outweigh the possible risk of cross-sensitivity. Recently, a desensitization protocol similar to that used for sulfonamide antibiotics has been described.⁴

By Wendy Smith, PharmD

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