MetaStar, under its contract with the Centers for Medicare & Medicaid Services, has embarked upon a project to decrease the rate at which potentially inappropriate medications (PIMs), and drug combinations implicated in drug-drug interactions (DDIs), are prescribed to Wisconsin Medicare beneficiaries.

The Medicare Modernization Act of 2003 directs Medicare Quality Improvement Organizations (QIOs) like MetaStar to offer quality improvement assistance pertaining to prescription drug therapy to providers, practitioners, Medicare Advantage organizations, and prescription drug plan sponsors offering prescription drug plans under the Part D drug benefit.

In a previous project with 1 drug plan, MetaStar sent mailings to physicians who recently had prescribed, and pharmacists who recently had filled prescriptions for, 1 of 4 PIMs: amitriptyline, cyclobenzaprine, glyburide, and propoxyphene. The mailings detailed the adverse effects of the 4 drugs and recommended pharmacologic and nonpharmacologic alternatives to their use. Data showed that the rate of use of these PIMs by Medicare beneficiaries enrolled in the drug plan dropped from 8.2% to 4.7%, and rate of prescribing of these PIMs to beneficiaries in the plan fell from 12.3% to 9.5%.

Buoyed by this success, MetaStar has undertaken a more ambitious project. We will be sending similar mailings to Wisconsin physicians for the purpose of decreasing the prescription of medications known to cause unnecessary risk in the elderly. The new project is different from the earlier project in important respects:

- The new project is aimed not only at medications that are potentially inappropriate by themselves, but also at medications known to cause risk in combination in elderly patients, particularly those involving warfarin.
- The project aims at decreasing PIM and DDI rates statewide, not just in a particular drug plan.
- The choice of targeted medications and medication combinations is based entirely on the frequency with which they are prescribed, according to Medicare Part D claims.

There will, of course, be instances where recommended alternatives to PIMs and DDIs will carry their own risks, which physicians should weigh according to their clinical judgment. There also will be instances in which a physician may reasonably conclude that some suspect drugs and drug combinations are necessary in the care of a patient, despite the risks. MetaStar’s mailings will review the appropriate methods to manage patients who are prescribed such medications.

A brief discussion of each of the drugs and drug combinations we are targeting follows.

**Potentially Inappropriate Medications**

*Propoxyphene*—The updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults states that propoxyphene offers few analgesic benefits over acetaminophen, yet has the adverse effects of other narcotic drugs. Such effects can include central nervous system depression, sedation, and hallucinations. Propoxyphene can also further constipation, leading to problems associated with urinary incontinence as well as gastrointestinal complications. There are several treatment alternatives available for elderly patients: non-drug therapy such as hot or cold compresses, acetaminophen given around the clock, non-steroidal anti-inflammatory drugs (NSAIDs), tramadol/acetaminophen, or immediate-release opioid analgesics such as morphine. Although some of these agents are associated with many of the same adverse effects as propoxyphene, they tend to have a shorter half-life, making it easier to manage potential adverse effects.

*Nitrofurantoin*—This drug is commonly used to treat urinary tract infections in women. It is listed on the Beers list of potentially inappropriate medications in older adults, which cites the potential for renal impairment and the existence of

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safer alternatives. There also is a risk of chronic pulmonary reactions, particularly in patients receiving long-term nitrofurantoin therapy. Other side effects of nitrofurantoin can include nerve damage, anemia, nausea, vomiting, vertigo, fever, and rash; these side effects are more common in the elderly. In general, trimethoprim-sulfamethoxazole is the recommended drug of choice for uncomplicated cystitis, with an alternative being a quinolone (eg, ciprofloxacin). Nitrofurantoin should be reserved for when these other antibiotics are contraindicated, or in a locale where resistance to the other antibiotics is substantial. Elderly patients are more likely than younger patients to have decreased renal function, so if nitrofurantoin is to be used, care should be taken in dose selection, and it may be useful to monitor renal function in such patients.

Cyclobenzaprine—A common treatment for muscle spasms related to painful, acute musculoskeletal conditions, Cyclobenzaprine is listed on the Beers list—among other muscle relaxants and antispasmodics—pointing out that all are poorly tolerated by elderly patients. These drugs cause anticholinergic adverse effects (eg, dizziness, dry mouth, and constipation), as well as sedation and weakness. Such anticholinergic effects have been associated with falls and fractures in elderly patients. Pharmacokinetic studies have shown that steady-state plasma concentrations of cyclobenzaprine in elderly subjects were twice as high as in young subjects. Hence, many older patients cannot tolerate doses that generally are recommended: documented case reports of hallucinations, insomnia, and paradoxical excitement have occurred in elderly patients taking generally recommended doses. The effectiveness of cyclobenzaprine and other muscle relaxants at doses that are tolerated by elderly patients is questionable. Alternative treatment options include non-drug therapy such as hot or cold compresses, physical therapy, or NSAIDs.

Estrogens—The Beers criteria include “estrogens only (oral)” as a potentially inappropriate medication in elderly women. The list cites evidence of the carcinogenic (breast and endometrial cancer) potential of these agents, and the absence of cardioprotective effects in older women. Other adverse effects of estrogen include an increased risk of venous thromboembolism, stroke, and possibly gallbladder disease and dementia. While the severity rating for this medication is listed as low, claims data indicate that Premarin® in particular is commonly prescribed for postmenopausal women. The United States Preventive Services Task Force recommends against the routine use of combined estrogen/progesterin for the prevention of chronic conditions in postmenopausal women, and of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. If physicians are considering the use of hormone therapy (eg, for the management of menopausal symptoms), they should use a shared decision-making approach with the patient and take careful consideration of risks and benefits. In such cases, some expert groups recommend using the lowest effective dose for the shortest possible time.

Drug-drug Interactions
By far, the largest number of potentially dangerous drug combinations involve warfarin. The potential dangers tend to follow a similar pattern: A patient taking warfarin is started on another medication that potentiates it, and without suitable adjustment, the patient’s international normalized ratio (INR) rises. This leads to increased risk of hemorrhage and subsequent related adverse events. Similarly, if a patient taking warfarin and another of these medications has his/her dose of the latter medication reduced or stopped, there is a risk that the INR may fall to a subtherapeutic level.

According to Part D claims, the most common drug interaction involving warfarin is that between warfarin and levothyroxine. Other potentiaters that commonly are prescribed along with warfarin are amiodarone, cimetidine, and a number of antimicrobials, including trimethoprim-sulfamethoxazole, ciprofloxacin, and levofloxacin; studies conflict as to whether the warfarin/azithromycin interaction is clinically significant.

Physicians considering prescribing 1 of these medications to a patient on warfarin should consider the following:

- If the patient can do without the second medication, or without anticoagulation.
- Substituting for the second medication a medication that would accomplish the same goal without potentiating warfarin. For example, another H2 blocker might be prescribed instead of cimetidine.
- Decreasing the dose of warfarin, carefully monitoring INRs, and watching patients for signs of bleeding.

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References
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