Drug Monitor

Gout Treatment: Complex and Challenging

More than 90% of patients with gout may be getting contraindicated medicines, according to a study from the VA in New York and New York University. The principal conclusion: Patients with gout typically have multiple comorbid conditions; they tend to have numerous, "often strong," contraindications to the drugs available for gout management, and many are prescribed such medicines despite those contraindications.

The researchers say this is, to their knowledge, the first formal investigation of traditional gout medications and their use in patients with contraindications. Strikingly, medications used to treat acute and chronic gout generally have well-described contraindications, the researchers point out, but studies have not addressed the prevalence of those contraindications among patients with gout. In their study, 575 patients with gout were stratified according to the *International Classification of Diseases, 9th Revision,* Clinical Modification code (cohort I), American College of Radiology criteria (cohort II), and crystal diagnosis (cohort III).

Most patients had at least 1 contraindication to 1 of the commonly used gout therapies, and many had contraindications to more than 1 therapy. Of the 94% of patients in cohort I who had at least 1 contraindication to nonsteroidal anti-inflammatory drugs (NSAIDs), for instance, 18% were prescribed those agents, including 9% with a strong contraindication. Approximately one-fifth of patients in cohort I, one-fourth of patients in cohort II, and one-third of patients in cohort III received allopurinol despite contraindications. Colchicine was strongly contraindicated in more than 40% of the study patients.

Although they used FDA criteria to define drug contraindications, which allowed for a "rigorous external standard," the researchers say, they did not address drug-drug interactions, nor did they address the extent to which multiple moderate contraindications to a single drug might collectively constitute a strong contraindication. Therefore, they say, their data not only did not overestimate, but, in fact, may have underestimated the frequency of contraindications.

The researchers say that, during medical record review, they identified some reasons why physicians prescribed drugs despite contraindications. Physicians may "feel compelled to make the best drug choice from among a limited palette of available agents, based on clinical scenario," they say. Thus, 1 physician prescribed prednisone over colchicine or NSAIDs in a patient with diabetes and renal insufficiency, apparently preferring to risk steroid-induced hyperglycemia rather than NSAID-induced renal failure or colchicine toxicity.

However, other reasons for prescribing contraindicated drugs included failure to recognize the presence, nature, or severity of the contraindication(s), the researchers conclude, testifying to a need for more professional and patient education, as well as for alternative gout therapies with fewer or different contraindications. They cite the recent approval of the nonpurine xanthine oxidase inhibitor febuxostat, pegylated uricase, and a new dosing schedule for colchicine as potentially useful alternatives.

Source: *Am J Med.* 2011;124(2):155-163. doi:10.1016/j.amjmed.2010.09.012.

Comparing Conservative and Liberal Opioid Treatment

Comparing 2 different opioid treatments in 575 patients admitted to the chronic pain unit at the VA Greater Los Angeles Healthcare System, researchers found that even in "carefully selected" tertiary-care patients, substance misuse is a significant problem. Importantly, they add, 40% of the problems were not apparent within the first 6 months.

Patients were assigned to 1 of 2 groups: a conservative "hold the line" stable-dose group or a more liberal escalating-dose group. For the stable-dose group, medication increases were kept to a minimum, with the target of a steady dosage over the 12 months of the study. Medications only were increased when deemed medically necessary. Patients who reported inadequate pain relief were given options, such as increasing adjuvant medications, or were encouraged to use coping skills, such as exercise. Patients in the escalating-dose group, who reported inadequate pain relief, were given those nonopioid/nondrug choices, but also a moderate increase in dose, as well as the option of switching from short-acting to long-acting medication. Medication was not increased in cases in which it would be medically or ethically irresponsible, based on adverse effects or possible substance abuse. The 3 primary outcomes were improvement in usual pain levels, pain relief from medications, and improvement in function.

Although, in general, the study revealed no statistically significant differences in the primary outcomes between the 2 groups, the escalating-dose strategy did lead to "modest"

Continued on page 38

Continued from page 36

improvements in self-reported acute relief without an increase in misuse, compared with the stable-dose strategy. The escalating-dose group showed an 80% increase in dosage over the 12 months, compared with only a 16% increase in the stable-dose group. The pattern of results suggests that patients in the escalating-dose group, who had access to higher doses of the medication, experienced larger, immediate decreases in pain after taking medication than did those in the stable-dose group. However, the acute effect of medication dose did not seem to last, the researchers say, and did not translate into any group differences in usual pain scores or general functioning.

About 27% of patients were discharged over the course of the study due to opioid misuse/noncompliance, but the researchers found no group differences in the rate of opioid misuse. Dropout rates were similar in the 2 groups: 22 (33%) of the stable-dose group and 16 (26%) of the escalating-dose group were dropped due to opioid medication or clinic noncompliance. Substance misuse or noncompliance discontinuations were due to alcohol or illicit substance abuse in 13 patients (10%), noncompliance with medications in 20 (15%), or noncompliance with clinic procedures in 5 (4%). Most discontinuations were in the first 6 months: 30% in the first 2 months, another 30% by 6 months, and 5% in the last 2 months.

In terms of clinical practice, the study findings can be interpreted in 2 very different ways, the researchers suggest. On 1 hand, arguing against a liberal dosing strategy; despite the 80% increase in dose in the escalating-dose group, primary outcomes measures of pain severity and disability did not improve. The only "rather small" positive effects seemed to be due to acute relief. The lack of significant benefit, therefore, argues for a more conservative dosing strategy or even withdrawal of opioids altogether. The researchers also note, even in the stable-dose group, the clinicians had to increase the dose somewhat, which suggests tolerance is a significant problem even with conservative management.

An alternative interpretation, however, could be that, at least as practiced in this study, the liberal dose escalation protocol did not lead to increases in opioid misuse and did show a small but significant advantage in subjective ratings of pain relief. But because the liberal strategy included significant limitations on dose escalation, and because opioid adverse effects were not captured, the researchers caution against overgeneralizing to support greater opioid dosing as a general strategy.

This study is the first 1-year clinical trial assessing pain relief and substance misuse outcomes from opioid treatment of chronic, nonmalignant pain. Because it took more than 6 months for the bulk of the misuse to become evident, they suggest more long-term studies.

Source: *J Pain.* 2011;12(2):288-296. doi:10.1016/j.jpain.2010.09.003.

Easing a Common Problem in Cancer Patients

Amidotrizoate (AM) may be an important addition to cancer treatment, relieving one of the most troublesome and often inadequately treated problems: constipation. According to findings from a study of 99 patients with advanced cancer at La Maddalena Cancer Center and University of Palermo, both in Palermo, Italy, AM was effective and well tolerated. Patients receiving palliative care often have many factors contributing to constipation, including dehydration, metabolic changes, and concurrent medications.

The patients, who had had no bowel movements for 3 days, despite regular doses of senna or lactulose, were given a 50 mL oral dose of AM. Nearly half (44) of the patients had a bowel movement within a mean of 10 hours, and often reported significant improvements of other symptoms, such as nausea. The remaining 45 patients were given enemas; 2 responded within the next 24 hours. After a new dose of AM was administered to 14 patients, 7 of the patients responded positively.

The drug was well tolerated. Adverse effects were acceptable and ceased spontaneously within 24 hours. The most common adverse effect was diarrhea, reported by 19 patients. The researchers also point out that the oral medication means patients can avoid invasive and uncomfortable measures, such as an enema or manual evacuation.

The researchers say the drug, a hyperosmolar water-soluble contrast medium, was anise-flavored and generally palatable. AM, according to the researchers, was found to be an inexpensive and easy means to induce the bowel movement in about 45% of advanced cancer patients who experienced constipation, despite laxative treatment.

Source: *J Pain Symptom Manage.* 2011;41(2):421-425. doi:10.1016/j.jpainsymman.2010.04.022.