

# Some Opioids Safer Than Others in the Elderly

BY MARY ANN MOON

FROM ARCHIVES OF INTERNAL MEDICINE

The risks of opioid use for elderly patients with nonmalignant pain vary considerably by different agents and by different durations of use, according to an analysis of Medicare databases.

Patients taking codeine for more than 180 days are at increased risk for cardiovascular events, and those taking oxycodone or codeine for only 30 days are at increased risk for any-cause mortality, said Dr. Daniel H. Solomon and his associates in the rheumatology department and the pharmacoepidemiology division at Brigham and Women's Hospital, Boston.

"This study's findings do not agree with a commonly held belief that all opioids are associated with similar risk," the investigators noted.

They compared the safety profiles of different opioids for the treatment of nonmalignant pain in elderly patients because "relatively little attention has been paid" to this issue even though

the use of these drugs has risen by 50%-100% in recent years. In contrast, patients and physicians are relatively well informed about the toxicities of NSAIDs used for the same indications.

Dr. Solomon and his colleagues analyzed information in two states' Medicare databases of pharmaceutical coverage for low-income patients (mean age, 79 years) between 1995 and 2005. They matched 6,275 subjects who took five of the most commonly prescribed opioids for a variety of baseline factors using propensity scores.

Hydrocodone was used as the reference exposure, to which codeine, oxycodone, propoxyphene, and tramadol were compared.

The risk of cardiovascular events including MI, stroke, heart failure, revascularization, and cardiac death was similar across the five opioid groups after 30 days of use. However, by 180 days the cardiovascular risk with codeine was significantly higher (risk ratio 1.62) than with the other four opioids.

This finding is surprising and requires validation in other

study populations, the investigators said (*Arch. Intern. Med.* 2010;170:1979-86).

All-cause mortality was elevated after only 30 days of use for patients taking oxycodone (RR 2.43) or codeine (RR 2.05), but not for those taking other opioids.

In contrast, the risk of fracture of the hip, pelvis, wrist, or humerus was significantly reduced after 30 days of treatment for patients taking tramadol (RR 0.21) or propoxyphene (RR 0.54).

The risk of gastrointestinal adverse events – including upper GI bleeding, lower GI bleeding,

and bowel obstruction – did not differ across opioid groups.

These risks remained consistent through a range of sensitivity analyses either 30 days or 180 days and regardless of whether patients were taking low, medium, high, or very high doses of the drugs. ■

## Opioids Are Not 'Interchangeable'

VIEW ON THE NEWS

The findings by Dr. Solomon and his associates "challenge the conventional notion that the safety profiles of opioids are generally interchangeable" and carry two important clinical implications, said Dr. William C. Becker and Dr. Patrick G. O'Connor.

The first and most crucial implication is that the frequent use of codeine must be re-examined. "The untested but widespread assumption that codeine is safer from an addiction standpoint because of its lower potency may need to give way to these data demonstrating increased risk of cardiovascular events and all-cause mortality. If codeine is of middling efficacy for pain and is more risky than other opioids, there would be little reason to use it," they noted.

Secondly, the elevated risk of fractures with opioid use "has solid biological plausi-

bility" by two mechanisms of action: Opioids raise the rate of falls, and they suppress the production of androgen and estradiol, imperiling bone health. The study findings suggest that basic safety measures to counterbalance these effects are not being implemented.

"Efforts to improve patients' understanding of safe medication-taking practices, providers' understanding of safe prescribing practices, and standardization of safety-oriented follow-up are sorely needed," said Dr. Becker and Dr. O'Connor.

DR. BECKER AND DR. O'CONNOR are internists at Yale University, New Haven, Conn. They reported no relevant financial disclosures. These comments were taken from their invited commentary accompanying Dr. Solomon's report (*Arch. Intern. Med.* 2010; 170:1986-8).

# Central Neuronal Factors Seen as Key to Chronic Pain

BY MIRIAM E. TUCKER

EXPERT ANALYSIS FROM A WORKSHOP ON PAIN AND MUSCULOSKELETAL DISORDERS

BETHESDA, MD. – When it comes to managing chronic pain, Dr. Daniel J. Clauw said physicians have been looking in the wrong places.

"There is no chronic pain state where degree of damage or inflammation in the periphery correlates well with level of pain. Yet, the diagnostic algorithms or paradigms that everyone uses for treating chronic pain still assume that all pain is nociceptive. What we see in the peripheral tissues is not necessarily what our patients are experiencing," said Dr. Clauw, director of the chronic pain and fatigue research center at the University of Michigan, Ann Arbor.

Historically, it has been assumed that when there was a disparity between peripheral findings and pain, psychological factors were at work. But the current view of chronic pain is that while it may originate from peripheral nociceptive input or nerve damage, central neuronal factors – at least some of them genetically determined – are nearly always playing a role in leading to interindividual differences in pain sensitivity, which are in turn closely associated with clinical outcomes.

For instance, population-based studies have shown that 30%-40% of individuals with radiographic evidence of severe dam-

age from osteoarthritis are pain free, while 10% of those with normal radiographs have severe pain (*Br. J. Rheumatol.* 1997;36:726-8). Psychological factors explain very little of the variance between symptoms and structure (*Arthritis Care Res.* 1998;11:60-5), suggesting that central mechanisms involved in pain processing are at work, Dr. Clauw said at the workshop, sponsored by the University of Michigan and the National Institutes of Health.

Of course, individuals with osteoarthritis and rheumatoid arthritis will often have evidence of nociceptive input, while those with fibromyalgia have more prominent central factors. But no chronic pain state is solely due to any one of these mechanisms, he said.

"The scientific paradigm shift requires that we rethink everything from diagnostics and treatment approaches – which currently place an unjustified importance on treating peripheral factors," he said.

The new paradigm suggests that, regardless of the specific diagnosis, "central pain states" including fibromyalgia, rheumatoid arthritis, osteoarthritis, lupus, and low back pain all tend to share certain characteristics that can be better

assessed by asking questions than by physical examination.

Showing patients a body diagram and asking them to label all the areas where they have pain is a simple assessment tool for multifocal pain. Also, ask about previous pain and other somatic symptoms such as fatigue, memory difficulty, mood disorders, and sleep disturbances, all common in the context of central pain but not with pain that is solely peripheral.

Is the pain triggered or exacerbated by stressors, such as psychological stress, infections, or physical trauma? Was there a salient stressor in the patient's early life, such as an auto accident or the death of a loved one? All are common among patients with central pain, said Dr. Clauw, professor of anesthesiology and medicine (rheumatology) at the university.

Because these patients tend to have global sensory processing problems, asking about hypersensitivity to bright lights, odors, or noises will also help confirm the "central" diagnosis. Take a family history of pain as well, as there are strong familial and genetic linkages among the chronic pain syndromes, at least among women (*Psychol. Med.* 2009;39:497-505).

**'What we see in the peripheral tissues is not necessarily what our patients are experiencing' in terms of pain.**



DR. CLAUW

Physical examination is likely to be normal except for diffuse tenderness and nonspecific neurologic signs (*Arthritis Rheum.* 2009;60:2839-44).

"This is why, historically, patients with fibromyalgia haven't been believed," Dr. Clauw commented.

As for treatment, it is becoming increasingly clear that peripherally acting pharmacologic agents such as opioids, corticosteroids, and nonsteroidal anti-inflammatory drugs simply do not work in central pain states.

Far more effective for fibromyalgia – and most likely other central pain states as well – are dual reuptake inhibitors such as tricyclic compounds (amitriptyline, cyclobenzaprine), serotonin-norepinephrine reuptake inhibitors (milnacipran, duloxetine), gamma hydroxybutyrate, and gabapentin. There is also modest evidence supporting the use of tramadol, selective serotonin reuptake inhibitors, and dopamine agonists (*JAMA* 2004;292:2388-95).

Nonpharmacologic therapies are also beneficial, including cognitive-behavioral therapy, exercise, and sleep hygiene (*Best Pract. Res. Clin. Rheumatol.* 2003;17:685-701).

Dr. Clauw disclosed that he is a consultant for Pfizer, Forest, Eli Lilly, Pierre Fabre Laboratories, Cypress Biosciences, Wyeth, UCB, AstraZeneca, Merck, Johnson & Johnson, Nuvo, and Jazz. He said he has also received research support from Pfizer, Cypress, and Forest. ■