

Central Neuronal Factors 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 damage 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.



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

DR. CLAUW

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

assessed by asking questions than by physical exam.

Showing patients a body diagram and asking them to label all the areas where they have pain is a simple assessment tool for multifocal

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).

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, serotonin-norepinephrine reuptake inhibitors, gamma hydroxybutyrate, and gabapentin.

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. ■

Opioid Safety Varies in Elderly With Nonmalignant Pain

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, a study has shown.

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 mortality due to any cause, said Dr. Daniel H. Solomon and his associates in the rheumatology department and the pharmacoeconomics 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 increased 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 were able to match 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, but by 180 days the risk with codeine was significantly elevated (risk ratio, 1.62), compared 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 – which included upper or lower GI bleeding and bowel obstruction – did not differ across opioid groups

at either 30 days or 180 days.

These risks remained consistent through a range of sensitivity analyses of the data. Importantly, the risks also were consistent regardless of whether patients were taking low, medi-

um, high, or very high doses of the drugs. “The risks were substantial and translated into numbers needed to treat that would be considered clinically significant,” Dr. Solomon and his associates wrote. ■

Opioids Not ‘Interchangeable’

These findings “challenge the conventional notion that the safety profiles of opioids are generally interchangeable” and carry two important 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 reexamined. “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.

Second, the elevated frac-

ture risk with opioid use “has solid biological plausibility” by two mechanisms of action: Opioids raise the rate of falls, and they suppress the production of androgen and estradiol, imperiling bone health. “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,” they said.

DR. BECKER and DR. O’CONNOR are with 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).

VITALS

Major Finding: The risks of opioid use in elderly patients vary substantially according to the specific drug used and the duration of use.

Data Source: A propensity-matched cohort analysis involving more than 31,000 Medicare patients.

Disclosures: This study was supported by the Agency for Healthcare Research and Quality. Dr. Solomon reported being an unpaid member of a celecoxib trial executive committee and an unpaid member of the data safety monitoring board for an analgesic trial, both sponsored by Pfizer.

VIEW ON THE NEWS