

## *Opioid complications after the treatment of non-cancer pain in geriatric patients: a call for pain specialists to be sophisticated clinicians*

With the suggestion that opioids could be used for the treatment of non-cancer related pain (1), the principles of the analgesic ladder were eventually implemented in patients with non-cancer pain (2) and since recent studies have highlighted the potential side effects and complications associated with the use of non-steroidal anti-inflammatories (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors in the geriatric population (3), the use of opioids in the treatment of non-cancer pain increased without long-term studies fully evaluating, first, the efficacy in conditions such as osteoarthritis, and then, the potential risks of this approach. As evidence of this increased use, the National Health and Nutrition Examination Survey (NHANES) showed that in the United States, there was a 2.5% increase in the number of Americans using opioids from the 1988-1994 period (3.2%) to the 2005-2008 interval (5.7%) (4). Of these individuals, 7% were patients age 65 or older. Moreover, according to the White House action plan, the number of opioid prescriptions dispensed by retail pharmacies increased by an astounding 48 percent—to 257 million prescriptions between 2000 and 2009 (5). Since 3.61 billion prescriptions were filled in the United States in 2009 (6), then 7.12% of these prescriptions were for opioids. Consequently, opioid analgesics utilization among Americans, and particularly, in individuals 65 years and older has increased in the past 12 years and it is likely that this will also be the case in the rest of the world where there is a free access to opioid therapy. This trend will likely continue to increase as it is predicted that there will be an increase of 3.1%, from 40 million in 2010 to 54 million in 2020, in the population of >65 years of age. Moreover, the recently published guidelines (7) for the treatment of pain associated with OA from the American College of Rheumatology reinforce the use of opioids in the geriatric population once other measures have failed to provide analgesia and there is no option for surgical replacement. Thus, the review by Torres et al. in this issue of the Journal (8) is timely because it highlights the potential problems associated with long-term opioid therapy in the geriatric population.

There are two major long-term concerns with the use of opioids in the geriatric population: endocrine changes leading to osteoporosis and possibly to increase cardiac morbidity and mortality, and the metabolism of these agents and the resulting drug-drug interactions.

### ENDOCRINE CHANGES

Long-term opioid use decreases cortisol levels, which may be why some patients may experience lassitude and lack of energy after long periods of therapy. It is important not to confuse these symptoms with those seen when opioid therapy is first implemented (9).

The diagnosis is made by performing an adrenocorticotropin (ACTH) stimulation test and if a flat cortisol response is seen, consideration to withdraw opioid therapy or implementing corticosteroid replacement therapy are indicated. Additionally, opioids decrease the production of luteinizing hormone (LH), and follicle stimulating hormone (FSH), resulting in low testosterone, and estrogen levels, which in turn can cause sexual impotence and eventually osteoporosis and cardiac complications (10-16). This problem can be easily overcome in men by prescribing testosterone in either intramuscular or the gel form. However, reduced sex hormones are more problematic in women because of the increased risk of breast cancer after estrogen/progesterone replacement. Thus, a consult with an endocrinologist may be warranted to address the risk of osteoporosis with the use of bisphosphonates, calcium and vitamin D therapy. A more disconcerting issue is the risk of cardiac disease associated with hypotestosteronism, even in the geriatric population (15,16). As suggested by the epidemiological analysis of Solomon et al. (17) where the authors matched older adults with osteoarthritis who started analgesic treatment with an NSAID, a COX-2 inhibitor, or an opioid and found that in a cohort of about 12,000 patients, that the incidence risk of composite cardiovascular events (myocardial infarction, stroke, hospitalizations for heart failure, coronary revascularization, and out-of-hospital cardiac death) was higher after treatment with opioids than with NSAIDs or COX-2 inhibitors (17). These findings come as a big surprise, as up to now; opioids have been touted as not being associated with cardiac problems. But it appears that the hypotestosteronism that results from long-term opioid therapy, even in the geriatric population, may result in accelerated atherosclerotic disease (15,16). However, it is important to recognize that there are several limitations in this study. First, the authors analyzed typical practice data from a nonrandomized setting. Thus, these results may be biased by residual confounding, in which factors influence the prescription of a given opioid and the safety events in question. This potential confounding bias limits the causal inference and renders this a study of associations. Second, the study database was limited because it consisted of health care and pharmacy utilization data without information about cause of death from death certificates, pain levels, functional status, aspirin or tobacco use, or over-the-counter medication use. This may have led to some misclassification of exposures and outcomes. Third, the authors studied a group of older low-income adults living in the states of New Jersey and Pennsylvania. Thus, the generalizability of the results needs to be proved in other cohorts. Finally, the authors observed a limited number of events in several outcome-exposure relationships. Thus, their ability to prove the safety of a given opioid for a specific outcome is limited. Nonetheless, the strength in this study is in the numbers, and the epidemiologic methods used. Consequently, one should not ignore the signal of concern raised by the authors and a comprehensive evaluation of risk (hyperlipidemia and increase risk of prostate cancer) *versus* benefit (reversal of hypotestosteronism induced atherosclerosis progression) should be undertaken.

### **METABOLISM OF OPIOIDS AND THE RISK OF DRUG-DRUG INTERACTIONS**

The epidemic of adverse drug reactions and interactions, and the estimated cost of these problems is an increase source of concern in the US. Among a matched population of patients with and without exposure to a drug metabolized by the same enzymatic system as a concurrently taken opioid, the former had a significantly higher than average number of emergency department visits (0.46 *vs.* 0.43,  $p < 0.01$ ) and inpatient hospitalizations (0.13 *vs.* 0.12,  $p < 0.01$ ), as well as significantly longer average stays

in the hospital (0.54 vs. 0.47,  $p < 0.01$ ) (18). In light of these findings, it has become critically important for the clinician prescribing opioids to also consider the metabolic pathways of the available opioids, the enzymatic systems used in the hepatic and intestinal metabolism (19) by medications synchronously prescribed to treat other conditions, and the genetic characteristics of a patients that may yield rapid, slow, or poor metabolizers of different drugs, including opioids (20). When an opioid drug regimen is chosen, it is important to be cognizant of the potential for drug-drug interactions, as many opioids are metabolized by the enzymes that modify and break down 40 to 50% of all medications. These are the cytochrome P450 (CYP450) isoenzymes, and those primarily involved with opioid metabolism are the CYP2D6, CYP2B6 (methadone), and CYP3A4 (fentanyl) systems (21,22). Tramadol, oxycodone, hydrocodone, and codeine are converted to active metabolites by CYP2D6. Therefore, drugs that inhibit this enzyme will decrease their effects (23,24). In addition, other commonly used medications, including fluoxetine, haloperidol, and paroxetine, can inhibit CYP2D6 function resulting in a lack of pain relief (25). In contrast, morphine, hydromorphone, and oxymorphone are not metabolized by the CYP450 enzymes, and therefore, can generally be prescribed with medications metabolized by that enzyme family (26). This is particularly important in elderly individuals as a recent meta-analysis of 43 studies of short-term opioid use among patients over age 60 with chronic non-cancer pain found that these individuals had reductions in pain intensity and improvements in physical functioning, but at a cost of decrease in mental health functioning (27). Based on the results of this study (27), it is tempting to suggest that the decrease in mental health function may be, at least in part, due to these drug-drug interactions. However, the studies were not designed to determine if this was the case.

## CONCLUSIONS

Following the first report on the use of opioids for non-cancer pain in 1986, opioids were prescribed freely to individuals with chronic pain not responding to other forms of pharmacological and non-pharmacological therapy, as well as interventional procedures. Since then, several studies have emerged suggesting that there may be significant harm to patients receiving chronic opioid therapy. Consequently, clinicians utilizing opioids should be aware of the caveats and pitfalls of opioid therapy, particularly in elderly individuals.

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