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## Opioid Use Associated With Increased Risk of Adverse Events Among Older Adults

***Opioids appear to be associated with more adverse events among older adults with arthritis than other commonly used analgesics, including coxibs and non-steroidal anti-inflammatories, according to a report in the December 13/27 issue of Archives of Internal Medicine, one of the JAMA/Archives journals. In a second report assessing only opioid use, different types of drugs within the class were associated with different safety events among older patients with non-malignant pain.***

"In the United States, one in five adults received a prescription for an analgesic in 2006, accounting for 230 million prescription purchases; however, the comparative safety of these drugs is unclear," the authors write as background information in one of the articles. "Although the cardiovascular safety of nonselective nonsteroidal anti-inflammatory drugs (nsNSAIDs) and selective cyclooxygenase-2 inhibitors (coxibs) has been called into question, there is little comparable information about the third major analgesic group, opioids."

In the first report, Daniel H. Solomon, M.D., M.P.H., and colleagues at Brigham and Women's Hospital, Boston, examined the comparative safety of nsNSAIDs, coxibs and opioids among 12,840 Medicare beneficiaries who received at least one of these analgesics between 1999 and 2005. Using data from a large health care utilization (claims) database, the authors evaluated the occurrence of cardiovascular events (heart attacks, stroke and heart failure, among others), gastrointestinal events (GI tract bleeding and bowel obstruction), acute kidney injuries, toxic effects on the liver, as well as falls and fractures.

Opioid users experienced higher rates for most types of serious adverse events than patients taking coxibs or nsNSAIDs, and nsNSAID users experienced the lowest risks. For example, fractures occurred among 101 per 1,000 opioid users per year, compared with 19 per 1,000 per year among coxib users.

Coxibs and opioids appear to be associated with greater cardiac risks than nsNSAIDs, but use of opioids and not coxibs was associated with a greater risk of hospitalization or death than use of nsNSAIDs. Conversely, the risk of

gastrointestinal tract bleeding was reduced among those taking coxibs (12 per 1,000 per year, compared with 21 per 1,000 per year among those taking nsNSAIDs).

"Analgesics are used daily by millions of people; however, current data do not allow patients or physicians to determine which type of agent is safest. We compared nsNSAIDs, coxibs and opioids across a wide range of specific safety events and several composite safety events," the authors write. "Although nsNSAIDs pose certain risks, these analyses support the safety of these agents compared with other analgesics. The recent concerns raised about opioid use in non-malignant pain syndromes appear warranted on the basis of these data."

In a second article, Dr. Solomon and colleagues at Brigham and Women's Hospital studied only those Medicare beneficiaries who received opioids for non-malignant pain between 1996 and 2005. They compared the rates of adverse events after 30 and 180 days among 6,275 patients each taking one of five types of opioids: codeine, hydrocodone, oxycodone, propoxyphene and tramadol.

The risk of gastrointestinal adverse events remained similar for all the medications studied, and thirty days after beginning opioid therapy, the risk of cardiovascular events was also similar across all types. However, after 180 days, the risk of cardiovascular events was increased among those taking codeine. With hydrocodone as the reference point, risk of fracture was 79 percent lower among those taking tramadol and 46 percent lower among those taking propoxyphene. Compared with those taking hydrocodone, death from any cause was 2.4 times as likely among those taking oxycodone and twice as likely among those taking codeine.

"This study's findings do not agree with a commonly held belief that all opioids are associated with similar risk," the authors write. "The risks were not explained by the dosage being prescribed and did not vary across a range of sensitivity analyses. The risks were substantial and translated into numbers needed to treat that would be considered clinically significant. Our findings regarding cardiovascular risk were surprising and require validation in other data sets."

Proving a cause-and-effect relationship between types of opioids and adverse events requires an experimental rather than observation study design, they note, "but these results should prompt caution and further study."

In addition, a research letter, published in the same issue, found double the risk of cardiovascular events among patients followed for a median (midpoint) of 189 days after they stopped taking the analgesic drug rofecoxib during

off-drug follow-up of a clinical trial. Joseph S. Ross, M.D., M.H.S., of Yale University School of Medicine, and colleagues analyzed data from a clinical trial that became available through litigation. Twenty-two cardiovascular events and 23 deaths occurred among patients who had taken rofecoxib in the trial, compared with six cardiovascular events and nine deaths among participants who took placebo.

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Joseph S. Ross et al. Persistence of Cardiovascular Risk After Rofecoxib Discontinuation. *Arch Intern Med.*, 2010;170(22):2035-2036 DOI: 10.1001/archinternmed.2010.461