Sometimes the Journal of the AMA Gets It Wrong! And so do careless journalists.

By Richard "Red" Lawhern — March 21, 2018

On March 6, 2018, the Journal of the American Medical Association published a 12-month randomized clinical trial [2] [authors Erin E Krebs, Amy Gravely, Beth DeRonne, Elizabeth Goldsmith, and others] which compared opioids to non-opioid medications for treatment of moderate to severe osteoarthritis and back pain among 240 Veterans Administration patients. In the days since publication, the study has been picked up by popular online magazines and blogs under blaring, but incorrect, headlines. The trial supposedly “proves” that opioid pain relievers work no better than acetaminophen (Tylenol) or non-steroidal anti-inflammatory drugs (NSAIDs), and that the risks of opioids make them unacceptable in the treatment of these types of pain.

In reality, the trial proves no such thing. To an informed reader, the study is profoundly flawed on several grounds, despite the considerable effort that seems to have gone into study design and execution:

- The study addresses types of pain for which opioids have never been a preferred treatment of choice. The first line treatment is anti-inflammatory drugs (NSAIDs).

- The study protocols were flawed; the group set up two cohorts of patients in a “practical” trial that offered several medications in sequence until something was found that worked. About 11% of the patients in the “non-opioid” leg of the trial eventually tried tramadol (brand name Ultram) – an atypical opioid pain medication that was not identified as such in the study.
Patients on “non-opioids” were switched between medications an average of four to five times during the year of the study before a medication was found that worked. Patients on opioids either had successful therapy on the first medication tried or were switched only once. This difference was not detailed in the study results.

As noted by senior editor Jacob Sullum in a Reason Magazine blog,
“… the researchers excluded patients who were on long-term opioid therapy, which means they ignored people who had already found they did not get adequate relief from other treatments. It seems reasonable to assume that people who are currently using opioids to treat chronic pain are doing so because they think these drugs work better for them than Advil or Tylenol, and they may even be right to think that. If you exclude those patients from a study of pain treatment, you are excluding precisely the people who are most likely to get more relief from opioids.”

Observations of Stephen Nadeau, MD (a specialist in the treatment of chronic pain) in a private email to the author are also meaningful:
“The mean dose of opioid was 21 mg morphine equivalent (MEQ)/day and only 12.6% of patients randomized to the opioid group were on > 50mg MEQ/day. The operational clinical range for opioids used in the [the] treatment of chronic non-malignant pain is roughly 50-1000 mg MEQ/day [and yes 1000 is not a typo]. There are excellent scientific data on this, even as the CDC and others have avidly promoted a “one size fits all” concept and advocated for daily dosage of <90 mg MEQ (resulting in untold suffering and many deaths in the 1.6 million people with chronic pain and on doses of >90 mg MEQ/day).

“Variability in opioid dosing requirement is related to genetic variations in the mu-1 opioid receptor gene and to variability in opioid metabolism. Thus, the doses used in the Krebs trial were unlikely to be effective, even for the -- on average -- moderate pain that characterized this population. Bottom line conclusion: insufficiently titrated doses of opioids are not superior to non-opioid alternatives in the treatment of chronic nonmalignant pain. We have known this for decades.”

“Three different antidepressants were specifically noted as alternatives for pain treatment in the non-opioid group. Just over 25% of the patients in this trial were at least moderately depressed. However, the authors do not provide data on antidepressant use in the two groups — a key omission. Antidepressants are highly effective in treatment of pain and can reduce the dose of opioids needed. Differences in outcome between the two groups relating to opioid use could have been masked by the use of antidepressants in the non-opioid group.

The bottom line is that the study seems to have set up to give a predetermined result: to discredit opioids in favor of NSAIDs and Tylenol. It was a bit like staging a race between some contestants in leg-irons versus others who ran after taking steroids for months.

Any of these biases alone should have disqualified the study from publication in JAMA, but the fact that three of them are found in the same paper raises suspicions, and rightly so. The fact that
JAMA editors let this piece see the light of day should have us all questioning the integrity and/or standards of the journal.

Richard A. Lawhern Ph.D. is a technically trained non-physician healthcare writer and social media moderator for chronic pain communities. He has over 20 years of hands-on experience as a patient advocate, with multiple publications concerning pain and public policy on medical issues. Dr. Lawhern is also an American Council advisor.