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# Mortality Increased With Long-Acting Opioids

Liam Davenport | June 17, 2016

Long-acting opioid medications are associated with an increased risk for death among patients treated for noncancer pain in comparison with patients treated with other pain medications, including gabapentin (multiple brands) and cyclic antidepressants, particularly in the first month after starting therapy, the results of a large US study reveal.

In a study of more than 45,000 prescription episodes, Wayne A. Ray, PhD, of the Department of Health Policy, Vanderbilt University School of Medicine, Nashville, Tennessee, and colleagues found that use of long-acting opioids was associated with a 90% increased risk for all-cause mortality. The risk was increased more than fourfold in the first 30 days of tratment.

The significantly increased mortality risk with the drugs held even after taking into account unintentional overdoses. The overall risk appeared to be partially explained by an increased risk for cardiovascular deaths.

Dr Ray told *Medscape Medical News* that the findings "reinforce the recent guideline by the Centers for Disease Control and Prevention that, for many patients, opioids should be a last resort for patients with chronic pain who don't have cancer or aren't in end-of-life or palliative care."

The research was published online June 14 in *JAMA*.

Commenting on these findings, William C. Becker, MD, an assistant professor of medicine at Yale University School of Medicine, New Haven, Connecticut, praised the study as "extremely well done" and noted "how we would want to look at this problem from a pharmacoepidemiology standpoint."

He said that the study "really adds to the growing understanding that long-acting opioids are risky and present relatively higher risks than other classes of medications for chronic pain, and, unfortunately, don't appear to offer much excess benefit to counteract that risk."

Both Dr Ray and Dr Becker agreed that the impact of long-acting opioids on mortality is likely to be greater in the "real world," given the fact that the majority of chronic pain patients have coexisting conditions and use several medications.

"The higher the baseline risk of the patient — in other words, the more comorbidities, the more serious disease — the greater the need to think carefully about starting a long-acting opioid," Dr Ray said.

Dr Becker noted: "If you look at actual practice, a third of our patients with chronic pain either have a history of drug abuse or current [drug abuse], so if we think about the excess risk among those folks, it's probably underestimated in this study, and that's the reality of real practice."

He added: "Real-life practice probably paints an even less flattering picture of long-acting opioids."

To compare all-cause mortality between long-acting opioids and alternative medications for moderate to severe pain, the researchers examined data on Medicaid patients with chronic noncancer pain who were treated between 1999 and 2012 and who were not receiving palliative or end-of-life care.

They identified 23,308 new episodes of prescriptions for long-acting opioids and 131,883 new episodes of control medication prescriptions. Using propensity scoring, the team matched 22,912 long-acting opioid episodes with an equal number of control medication episodes.

The mean age of the matched patients was 48 years, and 60% were women. The most common chronic pain diagnosis was back pain (75% of patients), followed by other musculoskeletal pain (63%) and abdominal pain (18%). The most commonly prescribed study medications were morphine SR, gabapentin, and amitriptyline (multiple brands).

For patients receiving long-acting opioids, during a mean follow-up period of 176 days, there were 185 deaths, compared with 87 deaths during a mean follow-up of 128 days for patients receiving control medications. The hazard ratio for mortality with

long-acting opioids was 1.64, at a risk difference of 68.5 excess deaths per 10,000 person-years.

Crucially, the risk for death was highest during the first 30 days after starting therapy, at a hazard ratio of 4.16 and a risk difference of 200 excess deaths per 10,000 person-years.

The increased mortality risk among patients receiving long-acting opioids was primarily attributable to out-of-hospital deaths, at a hazard ratio vs control medications of 1.90 and a risk difference of 67.1 excess deaths per 10,000 person-years. This translated into a hazard ratio for out-of-hospital deaths with causes other than unintentional overdose of 1.72 and a risk difference of 47.4 excess deaths per 10,000 person-years.

Patients taking long-acting opioids also had an increased risk for cardiovascular deaths compared with those taking control medications, at a hazard ratio of 1.65, or a risk difference of 28.9 excess deaths per 10,000 person-years.

Dr Ray believes that the question of whether noncancer pain patients should be taking opioids at all "would be worth reevaluating." Dr Becker said: "I really struggle with this question, because I do have patients who can do well on them." He added, "It's becoming apparent that the ones who do well are the ones maintained at lower doses."

Dr Becker noted that the median long-acting opioid dose at study entry was 50 mg morphine equivalents, which "is already pretty high." He said that "because of the way long-acting opioids are formulated...it's hard to use them without already starting on a moderate dose, [so] to use a long-acting opioid, you already have to get a patient in a moderate-risk category at the beginning of therapy.

"I would say unless we can find a way to make a long-acting opioid that is at a lower dose, which seems like it ought to be possible, then, yes, we ought to avoid prescribing them," he told *Medscape Medical News*.

Discussing the possibility of refraining from the use of opioids all together, Dr Becker observed, "If all we're getting out of opioids is excess harm," then "just taking them away would be a net gain to overall health."

He argued that the best approach to achieving long-term functional improvement is using nonpharmacologic therapies and addressing comorbidities. However, he feels that there is a lack of incentives in the United States for this kind of approach from a "treatment system standpoint."

For example, he pointed out that many alternative therapies to long-acting opioids are not covered by health insurance, and the in-depth assessments necessary to administer these therapies appropriately are not reimbursed.

Dr Becker said: "There are effective ways to treat chronic pain, it's just going to take quite literally a system overhaul to make sure that our incentives to provide that kind of care are aligned with reality."

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