Duloxetine for Subacute Pain Management after Total Knee Arthroplasty

Should We Write It Off or Reevaluate?

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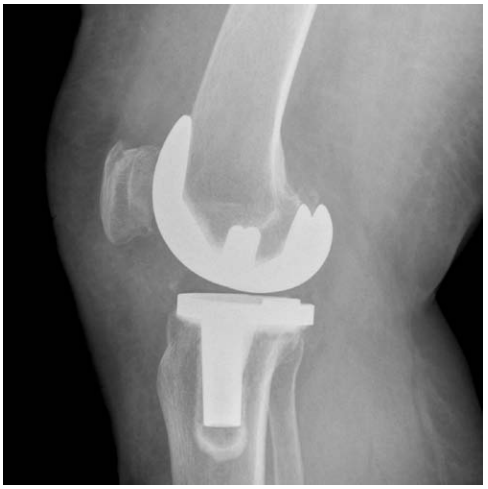
ALL actions have predictable and unpredictable consequences. As a result of the confluence of the rapidly escalating costs of conducting randomized controlled trials and the decline in federal research funding, industry has munificently stepped in to fill the gap. But whereas this has led to some major breakthroughs in pain medicine, it comes at a price. Industry-sponsored studies are 3.6 to 4 times more likely to yield positive results than non–industry-sponsored studies, which is a figure that is even further skewed by publication bias.[1] In contrast to large pragmatic and comparative-effectiveness studies that seek to measure benefit in real-life circumstances, the objectives of efficacy studies are intricately tied to those of the stakeholders (*i.e.*, companies) that sponsor them and generally focus on teasing out small effect sizes in an ideal patient population (*i.e.*, those with short duration of pain, moderate disease burden, not taking opioids, no coexisting psychosocial issues, *etc.*) that rarely reflects those encountered in clinical practice. Yet, even under these idyllic circumstances, the difference separating the treatment from placebo group is usually very small, averaging around 10 to 20% in studies evaluating duloxetine for knee osteoarthritis.[2,3] Whereas a two-point or 30% diminution in pain has been shown to constitute a clinically meaningful reduction on an individual basis, these same Initiative on Methods, Measurement and Pain Assessment in Clinical Trials guidelines note that smaller differences between groups can be considered clinically relevant in clinical trials.[4] Therefore, a non–industry-sponsored, blinded study that seeks to determine efficacy in a real-world population is greatly needed, and the authors should be applauded for undertaking this endeavor.



"[The authors] sought to determine whether duloxetine improves sub-acute pain after total knee arthroplasty."

In this issue of Anesthesiology, in a triple-blinded, placebo-controlled study, YaDeau *et al.*[5] sought to determine whether duloxetine improves subacute pain after total knee arthroplasty (TKA). Duloxetine is approved by the U.S. Food and Drug Administration for the treatment of chronic musculoskeletal pain, including osteoarthritis and low back pain, and has been shown in controlled trials to reduce pain and opioid consumption in a perioperative setting,[6,7] including a study that examined the effect of two doses given before and after knee replacement.[6] Hence, the hypothesis proposed by YaDeau *et al.*[5] was a sound one.

Arthritis is one of the three leading causes of disability,[8] so it is not surprising that the rate of TKA is rapidly rising in our aging population. There are over 700,000 TKA procedures performed annually, making it the most common surgical procedure associated with a hospital stay.[9] Between 1991 and 2010, the volume of primary TKA in the United States increased over 160%.[10] Importantly, TKA is cost-effective and improves functional status and quality of life.[11]

Answering the question proposed by YaDeau *et al.*[5] carries the potential for far greater implications than merely reducing postoperative pain and opioid use because there is a growing body of literature suggesting that rehabilitation may improve arthroplasty outcomes and that pain control without limiting adverse effects, such as sedation, can improve rehabilitation.[12] To test their hypothesis, 106 patients were randomized to receive either duloxetine or placebo for 15 days, starting on the date of surgery. Patients in both groups also received a comprehensive multimodal analgesic regimen, which included neuraxial anesthesia, epidural analgesia, adductor canal block, meloxicam, and oxycodone/acetaminophen as needed. Although patients on duloxetine did reduce their opioid use, the primary outcome of pain with ambulation, as well as pain at rest, did not differ significantly from placebo 2 weeks postoperatively.

One of the many strengths of this study is that it was triple blinded, and the investigators evaluated a proven drug in

Image: Thinkstock Image.

Corresponding article on page 561. This editorial discusses an off-label use of a U.S. Food and Drug Administration–approved medication.

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a clinically meaningful context for a condition in which there is little available information. Whereas the number of knee arthroplasties has increased substantially, this increase has not been accompanied by a commensurate increase in the analgesic options that can facilitate earlier and longer ambulation. Choosing a functionally relevant outcome measure was both patient centered and insightful, as the 2-week postoperative period is a critical window during which rehabilitation may improve long-term results. For mechanical conditions such as joint pain, reducing pain during ambulation is more important than reducing pain at rest, although the latter is by far a more common primary outcome measure in clinical trials. Yet, choosing a primary outcome measure assessed at a cross-section in time may be less accurate than averaging multiple pain recordings (*e.g.*, by using an electronic device) and less relevant than measuring the trajectory of recovery or improvement. Despite the many strong points, several important limitations in study design may have yielded inauspicious results. It is likely that this study was underpowered, as pain scores in the duloxetine group were approximately 10% lower than those in the placebo group, and a 10% difference between treatment and control groups is not unusual for U.S. Food and Drug Administration–approved adjuvant pain medications.[13] As referenced earlier, this may have been due to reliance on industry-sponsored studies, where the patients are more stringently selected and the magnitude of effect is typically greater. This can result in failure to recruit enough patients (type II error), which can lead to the inappropriate dismissal of a potentially beneficial intervention with a favorable side-effect profile. In addition, many experts have argued that because the availability of "rescue" medications is an essential element in all perioperative pain trials, opioid use, rather than pain scores, should be the primary outcome measure.[14] Regardless of treatment allocation, all patients in this study received an effective, multimodal pain treatment regimen, which often translates into decreased postoperative pain. Well-controlled postoperative pain is less likely to become chronic postsurgical pain. As was pointed out in a previous Anesthesiology editorial on the ability of epidural analgesia to prevent phantom limb pain,[15] studies in which the control group receives very good perioperative analgesia are more likely to yield negative findings than those in which the control group receives suboptimal pain management.

The choice of dose provided to study patients (*i.e.*, 60 mg duloxetine daily) also deserves scrutiny. As the basis for this decision, the authors cited studies showing that 120 mg was not more effective than 60 mg for neuropathic pain.[16] However, postarthroplasty pain is generally inflammatory in nature, and even in *chronic* postsurgical pain after knee arthroplasty, only 6% of cases are predominantly neuropathic.[17] Previous randomized studies evaluating duloxetine for knee osteoarthritis used a dose range of 60 to 120 mg, suggesting that at least in some patients, the dosage studied may have been too low.[2,3,18]

In conclusion, we believe that while the study by YaDeau *et al.*[5] was generally well designed, pragmatic, and sought to answer an important question, the results should not be construed as definitive; instead, they should be used to inform more research into this area. As our population ages and opioid abuse continues to ravage communities, finding pain-reducing and opioid-sparing treatments for postarthroplasty pain is a worthwhile endeavor that we must continue to pursue.

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Competing Interests

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From Chloroform to Polyhymnia and Euterpe, Liebig's Muses of Hymns and Music

The art *mousike* (Greek for "pertaining to the Muses") naturally embraced music itself, and "well-pleasing" Euterpe (*right*) was the Muse of Music. On this Italian card advertising a company cofounded by chloroform pioneer Justus von Liebig (1803 to 1873), Euterpe is depicted playing the double-reeded, double-piped aulos. Veiled next to her stands Polyhymnia ("many hymned"), the Muse of sacred forms of song, poetry, and dance. Her veil(s) preserved modesty, piety, and mystery. By including veils, scarves, or ribbons, Polyhymnia's art is arguably practiced today in both religious and secular circles, in modern sacred dance and Olympic rhythmic gymnastics, respectively. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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