

# Flipping the Paradigm

## From Surgery-specific to Patient-driven Perioperative Analgesic Algorithms

Chad M. Brummett, M.D., Daniel J. Clauw, M.D.

**I**N this month's edition of *ANESTHESIOLOGY*, Lunn *et al.*<sup>1</sup> take an important step toward the understanding and implementation of personalized perioperative medicine. Previous studies have demonstrated an association between higher catastrophizing scores (a dysfunctional cognition or thought pattern) and increased postoperative pain and opioid consumption. The authors randomized 120 patients with high pain catastrophizing to receive either escitalopram or placebo from the day before surgery to postoperative day 6. The study did not show a difference in the primary outcome of pain with ambulation 24h after surgery. This study is a timely follow-up to a recent systematic review that concluded that there was insufficient evidence to support the use of antidepressants in the treatment of acute pain.<sup>2</sup>

Mitchell Max<sup>3</sup> (1949–2008) is generally credited with first suggesting in 1990 that we could more successfully treat pain if we treated based on the underlying mechanism(s). At the time he initially proposed this idea, most in the pain field thought that we could progress rapidly in this regard, especially given the newly available genetic techniques that might help identify the basis for interindividual differences in pain mechanisms. This has been much more difficult than originally envisioned, but approximately 15 yr later, we are finally beginning to see evidence that this is possible. Despite early enthusiasm for polymorphisms of the opioid receptor (OPRM1), and other genes initially shown to affect pain or medication sensitivity, subsequent studies and meta-analyses have failed to replicate these findings.<sup>4,5</sup>

Other approaches to identifying different underlying mechanisms of acute or chronic pain in different individuals were simultaneously studied. For example, quantitative sensory testing (a.k.a., experimental pain testing) has been used for decades to identify differing underlying mechanisms of pain in



***“By flipping the paradigm, we can start with the individual aspects of the patient and then consider the surgical condition.”***

different individuals. Many studies have suggested that individuals with quantitative sensory testing evidence of aberrant pain processing require increased analgesics, especially in the perioperative period. In chronic pain patients, recent studies have shown that individuals with painful diabetic neuropathy with a quantitative sensory testing pattern suggesting decreased descending analgesic activity were more likely to respond to duloxetine,<sup>6</sup> and those that show a more “irritable nerve” pattern preferentially respond to oxcarbazepine.<sup>7</sup> This latter study was the first to *a priori* identify a cohort that they thought would preferentially respond to a specific analgesic and then stratify and randomize based on those criteria. Trials designed in this manner are methodologically superior to the enriched design used by Lunn *et al.*<sup>1</sup> which could not ascertain whether *all* patients receiving escitalopram might fare better when they are given a certain adjunctive analgesic regimen. However, quantitative sensory testing is currently cumbersome to perform in routine clinical practice, so this method of personalizing analgesia will likely be restricted to specialized settings where this testing can more easily be performed.

The use of patient-reported outcomes to “phenotype” individuals so as to infer differing underlying mechanisms of pain (such as was used by Lunn *et al.*<sup>1</sup>) has the highest likelihood of clinical translation because these methods are easy to incorporate into routine clinical practice. The authors chose to identify individuals with a highly specific psychological profile (catastrophizing) and posited that these individuals would preferentially respond to the highly selective serotonin reuptake inhibitor, escitalopram. Although their rationale for choosing individuals most likely to respond to escitalopram was sound, it could be argued that this was not the best antidepressant to use

Image: A. Johnson.

Corresponding article on page 884.

Accepted for publication November 3, 2014. From the Department of Anesthesiology, University of Michigan Health System, Ann Arbor, Michigan.

Copyright © 2015, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. *Anesthesiology* 2015; 122:731-3

as an adjunctive analgesic in this setting. It is generally felt that in both animal and human studies, antidepressants with both noradrenergic and serotonergic activity (*e.g.*, serotonin norepinephrine reuptake inhibitors or tricyclics) are superior analgesics to those with only serotonergic activity.<sup>8,9</sup> Moreover, it is now generally thought that the analgesic effect of a serotonergic/noradrenergic compound is largely independent of whether an individual is depressed or not because these drugs are likely exerting their analgesic effects by augmenting descending analgesic activity rather than by reducing depression.<sup>10</sup>

Although psychological factors are certainly important in pain, more recent studies have suggested that there are other identifiable phenotypic features that might be even more important in personalizing analgesic regimens. This may be particularly important when studying acute analgesic responses in individuals with ongoing chronic pain (*i.e.*, acute or chronic pain), such as those studied in the trial by Lunn *et al.*<sup>1</sup> There has been a recent recognition that subsets of any chronic pain cohort have “centralized” their pain, wherein central nervous system factors magnify and augment pain responses and markedly change the types of analgesics to which an individual will respond.<sup>11</sup> The best studied of these conditions is fibromyalgia, in which patients describe widespread body pain without any clear evidence of ongoing nociceptive input. If one considers that any individual with chronic pain is somewhere on a continuum from having pain purely due to ongoing nociceptive pain, to pain primarily due to central nervous system amplification of pain as in fibromyalgia, where an individual sits on this continuum is highly predictive of levels of pain and disability in nearly any musculoskeletal pain condition.<sup>12</sup> Because it is believed that fibromyalgia and other centralized pain conditions do not respond to opioids or surgical procedures and instead respond to centrally acting analgesics (*e.g.*, gabapentinoids, serotonin norepinephrine reuptake inhibitors, and tricyclics), stratifying patients based on these criteria might help to identify subsets of patients that would better respond to these latter drugs rather than our classic opioid-focused regimens. Our group has recently demonstrated this phenomenon: knee and hip arthroplasty patients with greater degrees of “fibromyalgia-ness” (which we infer is a crude measure of pain centralization) consumed markedly increased amounts of opioids in the perioperative period.<sup>13</sup> The fibromyalgia survey score was independently associated with more postoperative opioid consumption, whereas catastrophizing, depression, and anxiety were not. This does not mean that psychological factors are not important in acute and chronic pain, but instead that other central nervous system-mediated processes may be even more important.

Ultimately, we must shift the paradigm. Surgery-specific algorithms for perioperative care add value; however, such systems place the majority of the focus on the surgical condition rather than the most important factor—the patient. In many institutions, multimodal analgesia and regional anesthesia are applied in an all or nothing manner. Furthermore, the literature is biased to the reporting of large academic medical

centers, whereas studies that include smaller and private hospitals demonstrate huge variance in practice patterns.<sup>14</sup> By flipping the paradigm, we can start with the individual aspects of the patient and then consider the surgical condition. It may be that the inpatient perioperative algorithms can be focused on surgery, but given the continued high rates of acute and chronic postsurgical pain, we must consider trials that randomize high-risk patients to receive mechanistically based analgesics throughout their acute and subacute pain (*e.g.*, weeks of therapy rather than only as an inpatient).

Although the primary outcome of the study by Lunn *et al.*<sup>1</sup> was negative, the approach was an important next step in the anesthesiologist’s role in defining care in the surgical home. The authors have made major contributions to our understanding of acute and chronic postsurgical pain and are poised to continue to advance clinical care. Randomized controlled trials of high-risk populations identified by simple questionnaires are a logical next step in the study of acute pain, and we look forward to additional work from this prominent research team.

### Competing Interests

Dr. Brummett receives research funding from Neuros Medical Inc. (Willoughby Hills, Ohio). Dr. Clauw is a consultant for Pfizer, Inc. (New York, New York); Johnson and Johnson (New Brunswick, New Jersey); Forest Pharmaceuticals (New York, New York); Merck (Whitehouse Station, New Jersey); Nuvo Research, Inc. (Mississauga, Ontario, Canada); Eli Lilly, Inc. (Indianapolis, Indiana); Grunenthal Pharma Ltd. (Dublin, Ireland); Jazz Pharmaceuticals, Inc. (Palo Alto, California); and Purdue Pharma (Stamford, Connecticut). Dr. Clauw also receives research funding from Eli Lilly, Merck Pharmaceuticals, and Forest Pharmaceuticals.

### Correspondence

Address correspondence to Dr. Brummett: cbrummet@umich.edu

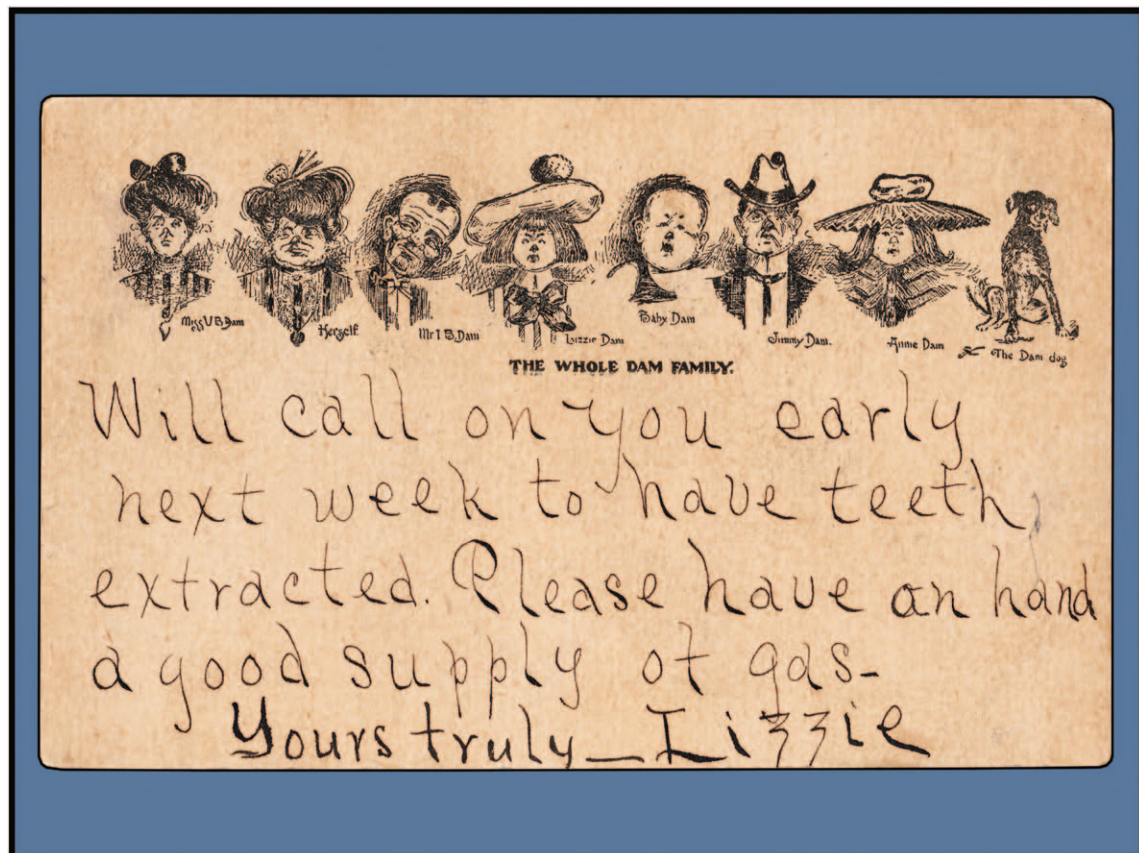
### References

1. Lunn TH, Frokjaer VG, Hansen TB, Kristensen PW, Lind T, Kehlet H: Analgesic effect of perioperative escitalopram in high pain catastrophizing patients after total knee arthroplasty: A randomized, double-blind, placebo-controlled trial. *ANESTHESIOLOGY* 2015; 122:884–94
2. Wong K, Phelan R, Kalso E, Galvin I, Goldstein D, Raja S, Gilron I: Antidepressant drugs for prevention of acute and chronic postsurgical pain: Early evidence and recommended future directions. *ANESTHESIOLOGY* 2014; 121:591–608
3. Max MB: Towards physiologically based treatment of patients with neuropathic pain. *Pain* 1990; 42:131–7
4. Walter C, Lötsch J: Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment. *Pain* 2009; 146:270–5
5. Klepstad P, Fladvad T, Skorpen F, Bjordal K, Caraceni A, Dale O, Davies A, Kloke M, Lundström S, Maltoni M, Radbruch L, Sabatowski R, Sigurdardottir V, Strasser F, Fayers PM, Kaasa S; European Palliative Care Research Collaborative (EPCRC); European Association for Palliative Care Research Network: Influence from genetic variability on opioid use for cancer pain: A European genetic association study of 2294 cancer pain patients. *Pain* 2011; 152:1139–45

6. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y: Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain* 2012; 153:1193–8
7. Demant DT, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup NB, Jensen TS, Sindrup SH: The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain* 2014; 155:2263–73
8. Dharmshaktu P, Tayal V, Kalra BS: Efficacy of antidepressants as analgesics: A review. *J Clin Pharmacol* 2012; 52:6–17
9. Otsuka N, Kiuchi Y, Yokogawa F, Masuda Y, Oguchi K, Hosoyamada A: Antinociceptive efficacy of antidepressants: Assessment of five antidepressants and four monoamine receptors in rats. *J Anesth* 2001; 15:154–8
10. Arnold LM, Hudson JI, Wang F, Wohlreich MM, Prakash A, Kajdasz DK, Chappell AS: Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with *versus* without major depressive disorder. *Clin J Pain* 2009; 25:461–8
11. Clauw DJ: Fibromyalgia: A clinical review. *JAMA* 2014; 311:1547–55
12. Wolfe F: Fibromyalgianess. *Arthritis Rheum* 2009; 61:715–6
13. Brummett CM, Janda AM, Schueller CM, Tsodikov A, Morris M, Williams DA, Clauw DJ: Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: A prospective, observational cohort study. *ANESTHESIOLOGY* 2013; 119:1434–43
14. Memtsoudis SG, Sun X, Chiu YL, Stundner O, Liu SS, Banerjee S, Mazumdar M, Sharrock NE: Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. *ANESTHESIOLOGY* 2013; 118:1046–58

## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

## Lizzie's Laughing Gas Request on a Dam Family Postcard



In 1905 the Edison Manufacturing Company released a popular 4-minute movie titled *The Whole Dam Family and the Dam Dog*. Not surprisingly, the Dam Family was then heavily merchandised to Americans, at least until the 1920s. As depicted on this postcard (above) from left to right, "The Whole Dam Family" consisted of the hair-playing "Miss U. B. Dam," the loquacious "Herself," the sneezing "Mr. I. B. Dam," the gum-chewing "Lizzie Dam," the crying "Baby Dam," the cigarette-smoking "Jimmy Dam," the blushing "Annie Dam," and the troublemaking "Dam Dog." Rather than by "Lizzie Dam," this postcard was addressed by a "Lizzie" of unknown surname to a Dr. J. E. Waitt of Boston. For her dental extraction, Lizzie requests that Dr. Waitt "have on hand a good supply of [laughing] gas." This postcard is part of the Wood Library-Museum's Ben Z. Swanson Collection. (Copyright © the American Society of Anesthesiologists, Inc.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.