Neuromodulation as an Alternative to Opioids in the Evolving Health Care Crisis

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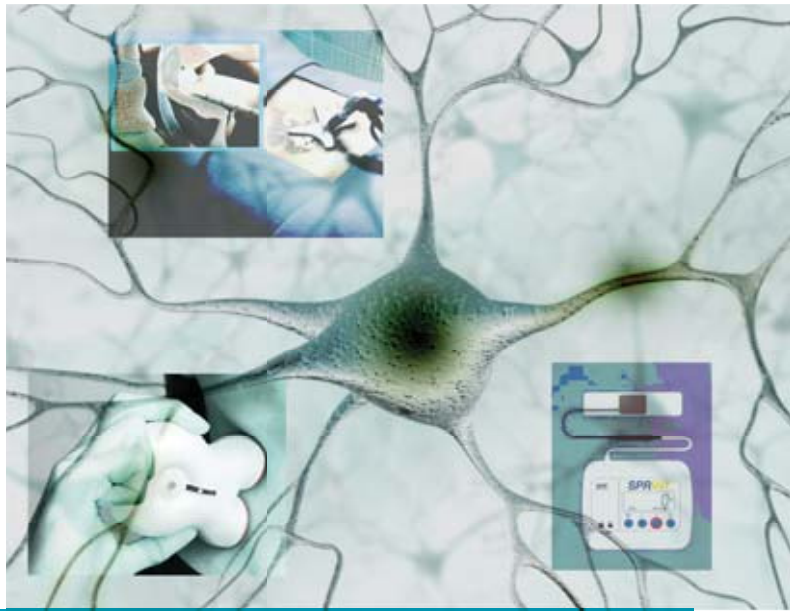
Dr. Staats has recieved research grants from Abbott, Boston Scientific, Grunenthal, Medtronic, Saluda, and Vertos; has patents licensed to NeurogesX; has stock or equity in ElectroCore Medical, Nalu, National Spine and Pain Centers, and SPR Therapeutics; and has consulted for Abbott, Grunenthal, Medtronic, Nevro, Saluda, and Vertos.



The opioid epidemic is the most pressing health crisis of our time. President Donald J. Trump; US Surgeon General John M. Adams, MD, MPH; Gov Chris Christie (R-NJ); and the CDC have called for more treatment for the addicted, greater awareness among clinicians, and stricter guidelines for prescribing opioids.

These strategies often involve offering treatment to those already addicted and providing funding for addiction after the problem has occurred. Although treating addiction is imperative, it is critical to understand and address the root cause of overprescribing in the United States. We must begin to prioritize pain therapy approaches within a treatment algorithm before the problem occurs. This involves using interventional strategies *prior to* opioids, and offering alternative strategies when low-dose opioid therapy is not enough.

Providers wrote nearly a quarter of a billion opioid prescriptions in 2016.[1] Although opioids are the most ubiquitous response to treating pain today, they have limited long-term efficacy data and are known to cause abuse, addiction, and death. Since 1999, the amount of prescription opioids sold in the United States nearly quadrupled, yet there has been no overall change in the amount of pain that Americans report, according to the CDC.[2]

In 1999, the Joint Commission made pain the "fifth vital sign," recognizing the problem of uncontrolled pain. However, we did not give physicians the tools to provide pain control safely and effectively. Rather, the medical community indicated to patients and physicians alike that patients would not become addicted to opioids, that opioids were safe and universally effective.[3]

Today, patients are still hurting. It is not enough to simply tell physicians to avoid opioids, as has been suggested by the "CDC Guideline for Prescribing Opioids for Chronic Pain," the surgeon general, and the president. Pain treatment requires a nuanced approach. It is important to put the risks of opioids into an appropriate

context, and to offer alternative treatment strategies to those suffering with acute and chronic pain (Figure).

Innovation will become ever more critical as we combat the opioid crisis. Many times, there are interventional therapies that physicians could and should employ before prescribing opioids. Conventional techniques, such as facet blocks, radiofrequency ablation, and other routine injections, have been around for decades and often are effective at reducing pain and opioid use while improving function. It is important that insurers recognize these approaches and not dismiss them as experimental.

These therapies should be used as a first line of defense, earlier in the pain treatment continuum, long before opioid use transforms into abuse. When earlier interventions—such as physical therapy, over-the-counter medications, or a short course of low-dose opioid therapy—fail, those patients should be referred to interventional pain specialists who have greater training and can consider a vast array of therapies as replacements for, or to minimize the use of, opioids.

Acute to Chronic Pain

Recent data, specific to acute pain, document the percentage of opioid-naive patients who remain on opioids chronically after 11 different surgical procedures. Compared with patients who have not used opioids before surgery, postsurgical patients who have undergone total knee arthroplasty (TKA) on opioids have the highest risk for chronic opioid use. Opioid use was considered chronic in previously opioid-naive patients who "filled 10 or more prescriptions or more than 120 days' supply of an opioid in the first year after surgery, excluding the first 90 postoperative days."[4] Many patients taking opioids before surgery continue to use opioids after arthroplasty.[5] However, persistent opioid use was not associated with change in joint pain. On the day of surgery, univariate analyses demonstrated that persistent opioid users at 6 months reported worse pain in their surgery site, greater functional impairment, more stiffness, increased overall body pain, more symptoms of depression, and higher levels of catastrophizing. There was no difference in those patients who continued to take opioids at 6 months based on age, sex, ethnicity, or type of surgery.

Furthermore, a univariate logistic regression revealed that preoperative opioid doses in oral morphine equivalents (OME) were significantly predictive of opioid use at 6 months. A plot of opioid dose on the day of surgery against the predicted probability of opioid use at 6 months shows that the probability of opioid use at 6 months increases as OME increases, with a presurgical OME of 60 or greater being associated with an 80% or greater predicted probability of opioid use at 6 months.[5]

Of 293 patients receiving 515 new opioid prescriptions in a 2009 study, 61 (21%) progressed to an episodic prescribing pattern and 19 (6%) to a long-term prescribing pattern.[6]

We *can* change this devastating trend and reverse the opioid epidemic. As physicians, we must first consider every suitable interventional strategy to treat pain before we turn to prescription opioids, regardless of their low up-front costs. We must also encourage greater physician education, private-sector innovation, and hospital and health insurance cooperation.

Evolving Field of Neuromodulation

Great advances are showing that precisely placed electrical fields, at specific targets, act like a drug. Traditionally, neurostimulation has been done with expensive, permanently implanted devices that are intended for long-term use. They are surgically implanted in an operating room with a patient under general anesthesia.

Last year, the FDA cleared a new peripheral nerve stimulation device, called SPRINT (SPR Therapeutics). This is a novel type of system that allows physicians to use a threadlike wire inserted near the nerves to stimulate specific nerve fibers, effectively turning off the pain sensation before it reaches the spinal cord. It is a minimally invasive neuromodulation option, intentionally reversible, drug-free, and provides sustained pain relief.

Multiple clinical trials have demonstrated the safety and effectiveness of this approach in managing chronic and acute pain. The device has been used to treat chronic pain in the back, joints, and extremities, and acute pain such as that after TKA. This therapy allows physicians the distinct ability to preferentially stimulate specific fibers within the nerves that modulate pain. The device is withdrawn without surgery at the end of the 60-day treatment period. Strategies such as this need 1) knowledge of indications and alternatives, 2) skill in placement, and 3) cooperation from third-party payors to facilitate reimbursement. Thus, this will prevent abuse before the patient takes his/her first pill.

A second electroceutical area that shows promise involves treatment of the vagus nerve with neurostimulation. gammaCore (electroCore) is a noninvasive vagus nerve stimulator recently cleared by the FDA for control of episodic cluster headaches. It has been shown to reduce pain without some of the side effects of systemic medications. These types of strategies need to be embraced and implemented before considering systemic opioid therapy.

Interventional Therapies for Chronic Pain

There are many strategies that need to be considered for chronic pain that have demonstrated efficacy, but are frequently delayed or not covered by insurers who consider the therapies experimental, or too invasive. Spinal cord stimulation with novel frequencies and dorsal root ganglion stimulation have multiple trials, with level 1 evidence demonstrating the efficacy of these therapies, some even suggesting opioid sparing.[7] The MILD procedure, a minimally invasive lumbar decompression, can correct certain types of spinal stenosis through a tube the size of a straw, removing the

source of pain with a 20-minute procedure.[8] A second procedure involves placing the Superion InterSpinous Spacer (Vertiflex) between the bones. Five-year data for this procedure have demonstrated excellent long-term pain control and function. It is imperative for the health of our nation for insurers to cover interventional pain management therapies, and not relegate them as experimental because of short-term cost savings.

Chronic Pain Patients Who May Need Controlled Substances

Unfortunately, some patients will need opioids. In today's world, pain cannot be denied, and injections and minimally invasive procedures are not always effective. Although our success rate is very high in avoiding opioids, minimally invasive surgery and even complex spinal procedures are not uniformly effective. Some patients will need to remain on opioid therapy long term. We do, however, need strategies to do this safely. We have learned that high doses of systemic opioids, use of opioids in conjunction with benzodiazepines, among other associated medical problems, carry a much higher risk for death.[9]

How do we confront this? Education needs to begin with primary care physicians, who prescribe more than 50% of opioids but often lack the formal and practical background to understand when, why, and for how long they should prescribe these narcotics. Many times, primary care physicians increase an opioid dose without pursuing alternatives that could limit the amount of opioids required to control pain.

Intrathecal therapy involves a pump delivering medications directly into the intrathecal space. The amount of medications required is much less than when delivered systemically. The chance of abuse is much less. The chance of diversion is minimal, and the possibility of an inadvertent overdose in an unmonitored setting can be minimized. These therapies have been shown to be more effective than systemic medications in patients with cancer, and there is no reason to believe the same is not true for patients with non–cancer-related pain.[10]

Additionally, alternative agents to systemic

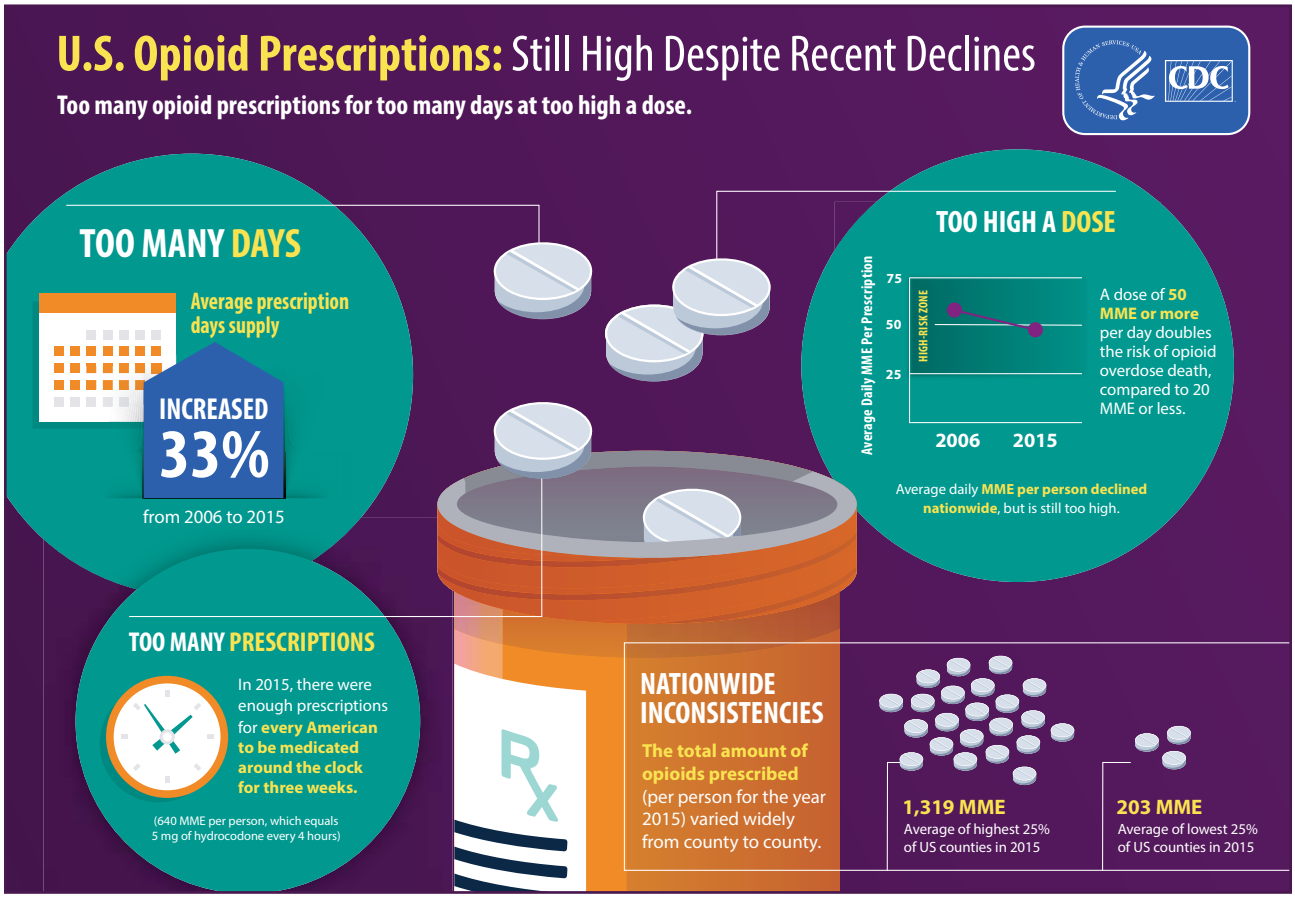


Figure. US opioid prescriptions: still high despite recent declines.

MME, morphine milligram equivalents

Source: CDC.

opioids—such as ziconotide (Prialt, Jazz Pharmaceuticals), clonidine, or local anesthetics—can be safely utilized and control pain in a very difficult population, minimizing dose escalation while improving pain control and function, without subjecting patients to the lifelong risk of systemic opioids.[11] Intrathecal therapy can mitigate the risks of systemic opioids. Unfortunately, because of insurance and reimbursement concerns, use of the therapy has been limited.

Stopping Addiction Before It Happens

Unfortunately, many innovative therapies that could otherwise provide hope to chronic pain sufferers are often labeled experimental by health insurance companies, regardless of strong data supporting their use. We can no longer allow for the platitude of experimental as a label. I, for one, am in favor of evidence-based medicine. When the term is used by third-party payors, it frequently facilitates denying what is perceived as expensive care, and is simply an excuse for not paying for innovative pain relief therapies.

Evidence-based medicine is defined as "the conscientious, explicit and judicious use of the current best evidence in making decisions about individual patients. The practice of evidence-based medicine means integrating individual clinical experience with the best available external clinical evidence from systematic research."[12] After all, there are far more positive data on many interventional pain alternatives than there are on the success of opioids.

Health insurance companies could learn from the German reimbursement system, which uses a vetting process to consider covering the cost of novel, more expensive therapies regardless of whether they are performed on an inpatient or outpatient basis; these applications are part of the NUB system (or "new examination and treatment methods"), when inpatient procedures are affected, or as part of the 137e process, when outpatient procedures similarly involve incorporation of new technologies.

In these systems, a government body, InEK, receives applications from academic research hospitals in support of promising new therapies. When approved for a defined period of clinical assessment, the value of new therapies can be assessed rigorously after which point the government can decide whether the therapy warrants continued coverage when made routinely available to the public. Private insurers are also able to leverage the technology under the same terms.

Hospital value analysis committees (VACs) also have a role to play in the opioid crisis by providing support for new and effective therapies. It is increasingly difficult for new technologies to make their way through the hospital purchasing and supply chain departments, especially while payors are discerning coverage and payment levels.

Improved payment options need to be offered to allow patients the chance to cover the cost of new non-opioid therapies or to partner with their physicians to appeal against payor denials and to get the attention of the insurance companies.

Significant money is already being allocated to a pain management system that is effectively broken. Opioids can be exceedingly expensive in patients on high doses, approaching $6,000 per patient every year![13] It is time for health insurance companies and hospital VACs to stop using opioids as a first-line approach to pain and move forward to promote innovative drug-free therapies, as the long-term cost savings to society are evident.

When given the choice of a treatment that could lead to drug addiction and even death versus safe, drug-free, and effective therapies, chronic and acute pain sufferers will choose the latter. It is time that pain specialists let their voices be heard and assure our ability to provide patients real options beyond opioids.

References

1. CDC. Vital signs: over doses of prescription opioid pain relievers—United States, 1999--2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487-1492.
2. CDC. Understanding the epidemic. www.cdc.gov/drugoverdose/epidemic/index.html. Accessed November 16, 2017.
3. Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med*. 1980;302(2):123.
4. Sun EC, Darnall BD, Baker LC, et al. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. *JAMA Intern Med*. 2016;176(9):1286-1293.
5. Goesling J, Moser SE, Zaidi B, et al. Trends and predictors of opioid use after total knee and total hip arthroplasty. *Pain*. 2016;157(6):1259-1265.
6. Hooten WM, St Sauver JL, McGree ME, et al. Incidence and risk factors for progression from short-term to episodic or long-term opioid prescribing: a population-based study. *Mayo Clin Proc*. 2015;90(7):850-856.
7. Levy RM. Neuromodulation: The "not-so-hidden" cure for the opiate crisis. *Neuromodulation*. 2017;20(6):519-524.
8. Benyamin RM, Staats PS, MiDAS Encore I. MILD® is an effective treatment for lumbar spinal stenosis with neurogenic claudication: MiDAS ENCORE Randomized Controlled Trial. *Pain Physician*. 2016;19(4):229-242.
9. Merrill JO, Von Korff M, Banta-Green CJ, et al. Prescribed opioid difficulties, depression and opioid dose among chronic opioid therapy patients. *Gen Hosp Psychiatry*. 2012;34(6):51-57.
10. Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared to comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol*. 2002;20(19):4040-4049.
11. Staats PS, Yearwood T, Charapata SG, et al. Intrathecal ziconotide in the treatment of refractory malignant pain: a controlled clinical trial. *JAMA*. 2004;291(1):63-70.
12. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312(7023):71-72.
13. Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. *Neuromodulation*. 2017;20(2):96-132.