Balancing the Risks and Benefits of Opioid Therapy: The Pill and the Pendulum

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Over the past 20 years, the medicinal use of opioids has swung back and forth like a pendulum. However, unlike Edgar Allan Poe’s classic short story, the likelihood of a last-second rescue seems remote. In the 1990s, a confluence of economic, medical, and governmental factors coalesced into a mutual driver of widespread prescription opioid use for chronic pain.1 The havoc wrought by this shift in prescribing practices ushered in the most devastating addiction crisis in US history. The ramifications of indiscriminate opioid prescribing are ubiquitous across the United States, and the statistics are grim. Last year in the United States, each day almost 200 people died from a drug overdose, and opioids were responsible for approximately two-thirds of the deaths. Although most medical literature focuses on prescription opioids, the number of people dying from illicit use recently surpassed that from prescription misuse, and recent data suggest that most people who misuse illicit opioids do so for chronic pain after losing access to prescriptions.2 These emerging phenomena suggest that the pendulum is swinging back toward more restrictive prescribing practices that have occurred in the wake of recent health care policy and regulatory changes.3 Yet, it is unclear whether these reactionary approaches to curtailing opioid prescribing will lead to a sustainable balance of the risks and benefits of opioids for adults with chronic pain.4

Many experts deem the opioid crisis to be a predictable consequence of increased awareness about the deleterious effects of inadequately treated chronic pain. Approximately 40% of Americans suffer from chronic pain, with 10% suffering debilitating pain.5 Available treatments provide relief to only a minority of patients. For example, among stringently selected patients with neuropathic pain prescribed first-line analgesics, only approximately 1 in 5 obtain meaningful benefit compared to a control treatment; in daily clinical practice, the number needed to treat for a single person to derive benefit is even higher.6

The statistics on overdoses are easily tabulated from first responder and emergency department statistics, and deaths from opioids are readily accessible from local and federal morbidity and mortality data. And the non-statistically quantifiable measures are poignant and indelible, such as television images of grieving widows and young children finding parents passed out or dead with needles in their arms. But statistics measuring the benefits of opioids for chronic pain are more difficult to assess, although the extant evidence does support long-term improvement in functional capacity.7 However, important questions remain including: (1) How are subjective benefits balanced against the risks of overdose? (2) What value does society place on a caregiver being able to financially and emotionally support their family? (3) How does one quantify savings in people who become less depressed and suicidal, function better, and possibly undergo less invasive treatments? There is an evolving body of literature in the form of randomized trials to suggest that judicious use of opioids may improve mood and increase function in selected individuals.7,8 Regarding the ability of opioids to reduce health care utilization and improve work productivity, although some randomized studies have reported long-term benefit,9 the evidence for these outcomes is predominantly negative or anecdotal,10 suggesting that these variables should be...
considered during decision making. In addition to the association between untreated pain and suicide, there are peer-reviewed research\textsuperscript{11} and media\textsuperscript{12} reports of patients driven to suicide because of forced opioid tapers, although these numbers are difficult to quantify.

Critics cite studies reporting that opioids are not more effective than other pain medications and remind us there is minimal evidence of long-term effectiveness.\textsuperscript{13} Yet, these criticisms can easily be turned against non-opioid analgesics. Most people receiving long-term opioid therapy have not experienced relief with other medications or can’t take them for safety reasons. Opioids have not been found to be efficacious in placebo-controlled trials for chronic noncancer pain beyond 16 weeks\textsuperscript{14} (although there is evidence for long-term improvement in quality of life),\textsuperscript{7} but neither have the majority of other analgesics. Opioids also have not been found to be efficacious for cancer pain beyond 12 weeks,\textsuperscript{15} and with the possible exception of cancer-related bone pain, there are no pathophysiologic differences between noncancer and cancer pain mechanisms to suggest a difference in responsiveness. This viewpoint has been repeatedly espoused by the US Food and Drug Administration (FDA).\textsuperscript{16} Moreover, the improved survival rates of cancer patients translate to a significant overlap in life expectancy between cancer-related and noncancer pain, such that up to 40\% of patients seen in some National Cancer Institute–affiliated pain centers are cancer survivors.\textsuperscript{17} The reasons for the lack of long-term efficacy data for opioids and other analgesics are complex but include the ethics of conducting studies in which patients receive a placebo for longer than the 12-week time frame the FDA requires for drug approval.\textsuperscript{18} According to the Department of Health and Human Services report on pain management best practices, the absence of data on the duration of opioid effectiveness should not be misinterpreted as a lack of effectiveness.\textsuperscript{19}

The risk of addiction is real, and when unidentified or inappropriately treated, the consequences can be fatal. The prevalence varies widely in studies, from less than 1\% to over 25\%, and is inextricably linked to the population being studied and the judiciousness of the prescriber.\textsuperscript{20} But in carefully selected populations, the incidence is low, less than 5\% according to one systematic review.\textsuperscript{21} A review cowritten by the director of the US National Institute of Drug Abuse reported that “rates of carefully diagnosed addiction have averaged less than 8\% in published studies,” with slightly higher rates when misuse and abuse are factored in.\textsuperscript{22}

In randomized trials—which contain stringent selection criteria—that have followed up patients longer than 16 weeks and reported adverse events, addiction is extremely rare, as can be found in the long-term studies summarized by Thornton et al.\textsuperscript{7} The observation that addiction is uncommon in carefully selected patients with chronic pain is supported by literature published over the past 3 decades by the National Institutes of Health, the Centers for Disease Control and Prevention, the Drug Enforcement Agency (DEA), and the FDA. Although there are several reasons for the wide discrepancies in reported addiction rates, the most likely and compelling one—similar to disparate treatment results for other pain therapies—is differences in patient selection (ie, higher with indiscriminate use and poorer understanding of the factors associated with opioid use disorder and lower with rigorous selection and better education). In other countries, liberalizing opioid restrictions has been found to be associated with increased prescribing patterns.\textsuperscript{23}

In the face of these seemingly mutually exclusive goals, how can the risk to benefit ratio of opioids be balanced? One potential approach is through precision medicine, which takes into consideration individual variability in genetics, lifestyle, and susceptibility to adverse effects. Optimizing the risk to benefit ratio of opioids requires questionnaires designed to stratify the risk of addiction and overdose, surveilling compliance, and measuring benchmarks of optimal outcomes. Currently available abuse-deterrent opioids prevent only certain types of abuse...
(eg, crushing sustained-release compounds), but functionally selective agonists may someday be available that have less addiction potential, thereby favorably altering this ratio. The decision to initiate opioid therapy should also include a frank discussion that includes written informed consent delineating the risks and benefits of treatment, setting realistic expectations and achievable treatment goals, and a mutually agreed upon discontinuation strategy.

Phenotyping, which involves classifying individuals on the basis of observable characteristics, can be used to assess risks and benefits but is in its infancy. For instance, elderly patients with nociceptive pain may be more likely to obtain long-term pain relief with opioids than younger people with nocicplastic (eg, fibromyalgia) or neuropathic pain. There is also a genetic component to this equation that includes the development of acute pain, transitioning to chronic pain, responsiveness to treatment, and the likelihood of development of opioid use disorder. Because these variables involve multiple genes and other factors, genetic testing is likely to be neither feasible nor cost-effective in the near future.

What might future predictive modeling look like? An algorithm could start with estimating the likelihood of benefit by performing prognostic infusion tests, which could compare escalating doses of short-acting opioids to an active placebo. This approach has been used for drugs such as ketamine and was described for opioids years ago. The downside of an opioid infusion test is that in most people, long-term therapy fails because of tolerance, hyperalgesia, or adverse effects, and an infusion does not predict these well. Yet, even identifying people unlikely to respond to opioid therapy (ie, negative predictive value) can be beneficial. A pretreatment intravenous opioid test can be combined with quantitative sensory testing, which is increasingly employed to predict treatment outcomes, and perhaps psychological screening. The latter is often used before spinal cord stimulation to determine patient suitability, but considering the relative risks of neuromodulation and long-term opioid therapy, some practitioners have begun to employ it before initiating long-term opioid therapy. Whereas these and other screening tools require more research to better refine their predictive value, particularly for opioid therapy, the conceptual appeal of screening tests is that they can provide quantifiable measures of potential benefit, and the thresholds for a positive test result can be modified on the basis of clinical factors.

Because the decision to start a given treatment involves weighing anticipated risks and benefits, predictive analytics should also better refine risk assessment. For instance, it is well known that impulsivity and poor coping skills are associated with substance abuse and addiction, but even the most comprehensive risk stratification instruments do not adequately address these factors. For example, in the Screener and Opioid Assessment for Patients with Pain - Revised questionnaire, the 2 questions that address impulsivity concern past arrests and violent confrontations, which happen to only a small proportion of patients addicted to prescription opioids (ie, those without financial resources and conflict resolution skills). Screening questions such as this may also foment socioeconomic bias and contribute to discrepancies in prescribing patterns (ie, access to care). According to a recent review, most opioid screening tools were either based on low-quality studies or demonstrated poor performance in discriminating high-risk from low-risk patients.

It is our experience that patient and physician expectations also play a critical role in outcomes. Whereas systematic reviews have found that opioid therapy is perhaps the most efficacious treatment for chronic pain of various etiologies with numbers needed to treat in the 2.5 to 4 range and an average pain reduction of around 30%, it rarely completely eradicates pain. A health care system that incentivizes fast and simple solutions is not an ideal treatment model for people with complex problems. The Institute of Medicine cites unrealistic expectations as a contributor to the increasing prevalence of chronic pain, and it has also been linked to opioid addiction and poor pain treatment satisfaction.
No system will ever be perfect, but we are progressing to the point whereby big data and predictive modeling will soon enable us to predict with reasonable accuracy the chance of success not only with opioids but with all pain treatments. When we reach this point, the question will then become, “How much time are doctors willing to devote and how much risk will they assume, not only for patients but also for themselves?” The solution cannot ignore the administrative and financial burdens faced by physicians. The decision not to prescribe opioids may have adverse financial (eg, fewer referrals, perverse incentives such quid pro quos for patients prescribed opioids to undergo expensive drug testing and procedures) and professional (eg, online patient complaints, low satisfaction scores) ramifications that need to be addressed. The growing administrative tasks required to prescribe opioids also make opting out of voluntary DEA registration an attraction option for many physicians, especially those at risk for burnout. On the flip side of this equation, having less time to spend on patient care can result in inadequate screening, education on proper use, and monitoring; this may be especially relevant in busy primary care settings and in emergency departments.

Weighing risks and benefits is an inherent part of living, and there will still be people who divert and develop opioid use disorder, although evolving screening methods will continue to refine selection and reduce risk. But for patients who have exhausted other options and doctors willing to put their patients’ best interests on par with their own, making case-by-case decisions based on probability modeling can provide long-term benefits for patients and society.

Conclusions
In summary, the surge in opioid use has resulted in a crisis of unprecedented proportions, which in turn has led to an equally unparalleled campaign to curtail their use, even in patients in whom the therapy has represented a lifeline. It is clear that there are still people receiving high-dose opioid therapy in whom the risks outweigh the benefits, and there is still work to do on the education front. However, it would be shortsighted to develop amnesia about why we are facing an opioid crisis, which stems partly from the fact that there were widespread calls across the regulatory spectrum, including from the Centers for Disease Control and Prevention, the FDA, the Federation of State Medical Boards, the American Medical Association, the National Institutes of Health, and even the DEA, to develop better tools—including opioids—to address the chronic pain crisis, which has independently been found to be associated with higher mortality. In an era characterized by numerous sources of information and online forums where people with “fringe” viewpoints can find thousands of like-minded individuals, the middle ground is shrinking, both in health care and politics, which often includes health care policy. Yet, for an issue as critically important to the world’s health as chronic pain, we should put our differences aside and strive to find a “middle way” that balances the benefits of opioid therapy with the risks—akin to the center position in the arc of the pendulum.

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