

MAYO CLINIC  
PROCEEDINGSBeyond Supply: How We Must Tackle the  
Opioid Epidemic

See also page 344

The opioid epidemic is the most important and most serious public health crisis today. The effects are reported in overdose deaths but are also starkly evident in declines in sense of well-being and general health coupled with increasing all-cause mortality, particularly among the middle-aged white population.<sup>1</sup> As exceptionally well described by Rummans et al<sup>2</sup> in this issue of *Mayo Clinic Proceedings*, the cause of the epidemic is multifactorial, including an overinterpretation of a now infamous *New England Journal of Medicine* letter describing addiction as a rare occurrence in hospitalized patients treated with opioids, initiatives from the Joint Commission directed toward patient satisfaction and the labeling of pain as the “5th vital sign,” the advent of extended-release oxycodone (OxyContin), an aggressive marketing campaign from Purdue Pharma L.P., and the influx of heroin and fentanyl derivatives.

To date, most initiatives directed toward fighting the opioid initiatives, and the focus of the discussion from Rummans et al, have targeted the “supply side” of the equation.<sup>2-4</sup> These measures include restricting prescriptions, physician drug monitoring programs, and other regulatory actions. Indeed, although opioid prescriptions have decreased from peak levels, the prevalence of opioid misuse and use disorder remains extremely prevalent (nearly 5%).<sup>4,5</sup> Further, fatal drug overdoses, to which opioids contribute to a considerable degree, continue to increase, with 63,000 in 2016 alone.<sup>6</sup> Thus, although prescription supply and access are necessary and important, we need to address the problem as a whole. To this point, for

example, the ease of importation and synthesis of very cheap and powerful alternatives (eg, fentanyl and heroin) and the lucrative US marketplace have contributed to the replacement pharmacy sales and diversion with widespread street-level distribution of these illicit opioids; opioid-addicted people readily switch to these illicit opioids.<sup>4</sup>

A complementary and necessary approach is to target the “demand” side of opioid use, namely, implementation of preventive measures, educating physicians, requiring physician continuing education for opioid prescribing licensure, and addressing why patients use opioids in the first place. Indeed, prevention of initiation of use is the only 100% safeguard against addiction; however, millions of patients remain addicted, and they need comprehensive, rather than perfunctory, treatment. Rummans and colleagues are absolutely correct in their delineation of the unwitting consequences of a focus on pain, given that a perceived undertreatment of pain fueled the opioid epidemic in the first place. They are correct to point out how effective pain evaluation and treatment are much more than prescribing and should routinely include psychotherapy, interventional procedures, and nonopioid therapies.<sup>2</sup> In addition, we have described the crossroads between pain and addiction as well as successful strategies to manage patients with both chronic pain syndromes and addiction.<sup>7</sup>

Rummans and colleagues also mention much needed dissemination of medication-assisted treatment (MAT; eg, methadone and buprenorphine) and the opioid overdose medication naloxone, and we agree with both of these measures. However, in addressing the demand side of the opioid epidemic, the focus

must be much more comprehensive. Viewing opioid addiction as a stand-alone disease without consideration of other substance use or comorbid psychiatric pathology provides only a limited perspective. Rather, dual disorders are the rule and not the exception, and thus addiction evaluation and treatment should also specifically focus on psychiatric symptomatology and comorbidity. Epidemiological evidence indicates that over 50% of individuals with opioid use disorder meet criteria for concurrent major depressive disorder.<sup>8</sup> Recent evidence from Cicero and Ellis<sup>3</sup> indicates that the majority of opioid-addicted individuals seeking treatment indicate that their reasons for use are for purposes of “self-medication” and relief of psychiatric distress. To expand on this concept, we have suggested that drugs, by targeting the nucleus accumbens, alter motivation and reinforcement circuits and change brain reward thresholds; this change results in profound dysphoria and anhedonia, which, in turn, lead to further drug use.<sup>9,10</sup>

Obviously, then, opioid addiction treatment should focus on diagnosing and assessing psychiatric comorbidity and monitoring of affective states and other depressive symptoms. However, a bigger problem might be the pretreatment phase, considering that, as Rummans et al note, only 10% of patients with opioid use disorder receive any treatment at all.<sup>2</sup> Resources have principally been devoted to mitigating the effects of acute opioid toxicity both before and during intervention in the emergency department. A principal means of medical stabilization has been overdose reversal with the  $\mu$ -opioid receptor antagonist naloxone, and efforts have been largely focused on dissemination of this agent. However, while increased naloxone use among the lay public, first responders, and medical personnel has been successful in reducing deaths, recidivism is high and increased naloxone use has not affected the problem as a whole.<sup>11</sup> Generally, when patients present to the emergency department, clinical experience dictates that opioid overdoses are considered accidental until proven otherwise, which, after stabilization, allows the physician to discharge the medically stable patient, the hospital to collect reimbursement, and the pharmaceutical company to raise prices (eg, naloxone prices increased by 400% from 2014 to 2016, for autoinjection formulations).<sup>12</sup>

In addition to the substantial costs associated with repeated naloxone administration and emergency department visits, recidivism is inextricably linked with another problem—the reason for overdose in the first place is not addressed. As mentioned earlier in this editorial, depression prevalence is high in patients with opioid use disorders. Strikingly, using nationwide data from US poison control centers, West et al<sup>13</sup> found that over 65% of opioid overdoses reported were indeed suicide attempts, and of completed overdoses, the percent of those characterized as suicides climbed to 75%. Thus, an “inconvenient truth” may be that many of these opioid overdoses presenting to emergency departments may be unrecognized suicide attempts and that many of the over 66,000 deaths may indeed be completed suicides. Thus, comprehensive evaluation and treatment become even more relevant.

Clearly, more thorough evaluations in emergency departments with comprehensive risk assessments are needed, especially given that these patients may be guarded about suicidal ideation in the first place.<sup>14</sup> Indeed, efforts to initiate buprenorphine in the emergency department, which independently is being investigated for its therapeutic effects on suicidal ideation, have spread; however, while abstinence outcomes are favorable at 30 days, the therapeutic benefit seems to disappear at both 6 months and 1 year.<sup>15</sup> This failure of opioid reversal treatment is important, especially given that at 1 year, 15% of patients rescued with naloxone had died.<sup>16</sup> Additionally, lack of psychiatric services and overcrowding at many emergency departments may preclude a comprehensive evaluation; however, target screening of all high-risk patients may identify patients with even hidden suicidal ideation and allow for appropriate triage.<sup>14</sup>

Most addiction treatment today is centered around time-limited settings without adequate follow-up.<sup>17</sup> Although MAT is an important addition to treatment for opioid addicts, it is generally not sufficient for long-term sobriety given (1) the relatively high rates of immediate and short-term treatment discontinuation and (2) that patients rarely are using just opioids.<sup>18</sup> In fact, regarding long-term outcomes, methadone may be the only MAT treatment that demonstrates superior abstinence rates, safety, opioid overdose prevention, and treatment retention.<sup>18</sup>

We recommend that future studies include random assignment to different treatment modalities, assessing abstinence with urine testing and other modalities, psychosocial outcomes, and overall level of functioning for 5 years.

In terms of treatment, we suggest a continuing care approach, viewing addiction as a chronic, relapsing disease, but higher quality data are needed.<sup>17</sup> For example, in most states, physicians with substance use disorders who are referred for treatment indeed undergo evaluation and detoxification, but they are also monitored for 5 years with frequent drug testing, contingency management, evaluation and treatment of comorbid psychiatric issues, and mutual support groups.<sup>19</sup> Outcomes are generally superior, with 5-year abstinence and return to work rates approaching 80%.<sup>17,19</sup> Notably, most of these programs do not allow MAT, yet opioid-addicted physicians do as well in the structured, supportive, long-term care model as physicians addicted to other substances.<sup>19</sup> Obviously, the threat of professional license sanctions may impel physicians to comply with treatment, but many of the aforementioned strategies including contingency management, long-term follow-up, comprehensive psychiatric evaluation, and mutual support have demonstrable evidence for addiction treatment in general.<sup>19</sup>

More resources need to be devoted to addressing the opioid epidemic, particularly on the prevention and also the demand side. Access to treatment is important, but more investment is needed in improving treatment including implementing 5-year comprehensive care programs.<sup>17</sup> Thus, we recommend that future studies involve random assignment to different treatment groups, focusing on urine drug test—confirmed abstinence, psychosocial outcomes, and overall functioning. Additionally, advances in neuroscience may allow for the development of novel therapeutics targeting specific neurocircuitry involved in reward and motivation (ie, moving beyond the single receptor targets).<sup>20</sup> A parallel can be drawn to the AIDS epidemic, in which massive basic science investments yielded novel effective therapies, which have now become standard of care and one of the world's great public health successes.<sup>21</sup> Resources focused on these interventions and reinvigorating drug education and prevention may prove fruitful in addressing this

devastating epidemic. Further, lessons from this epidemic may help us move beyond a specific “one drug, one approach” so that for future epidemics, irrespective of the drug involved, we would already have in place a generalizable framework that utilizes the full repertoire of responses and resources.

A. Benjamin Srivastava, MD  
Mark S. Gold, MD

Department of Psychiatry  
Washington University School of Medicine  
St Louis, MO

**Potential Competing Interests:** The authors report no competing interests.

**Correspondence:** Address to A. Benjamin Srivastava, MD, Department of Psychiatry, Washington University School of Medicine, 660 S Euclid Ave, St Louis, MO 63110 (a.srivast@wustl.edu).

## REFERENCES

1. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci U S A*. 2015;112(49):15078-15083.
2. Rummans T, Burton MC, Dawson M. How good intentions contributed to bad outcomes: the opioid crisis. *Mayo Clin Proc*. 2018;93(3):344-350.
3. Cicero TJ, Ellis MS. Understanding the demand side of the prescription opioid epidemic: does the initial source of opioids matter? *Drug Alcohol Depend*. 2017;173(suppl 1):S4-S10.
4. Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. *N Engl J Med*. 2016;374(2):154-163.
5. Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 National Survey On Drug Use and Health. *Ann Intern Med*. 2017;167(5):293-301.
6. Hedegaard H, Warner M, Miniño AM. *Drug overdose deaths in the United States, 1999-2016*. Hyattsville, MD: National Center for Health Statistics; 2017. NCHS Data Brief 294.
7. Bailey JA, Hurley RW, Gold MS. Crossroads of pain and addiction. *Pain Med*. 2010;11(12):1803-1818.
8. Grella CE, Kamo MP, Warda US, Niv N, Moore AA. Gender and comorbidity among individuals with opioid use disorders in the NESARC study. *Addict Behav*. 2009;34(6-7):498-504.
9. Srivastava AB, Gold MS. Does psychiatric illness cause drug abuse-addiction or vice versa? part I. *Directions in Psychiatry*. 2017;37:77-87.
10. Dackis CA, Gold MS. Opiate addiction and depression—cause or effect? *Drug Alcohol Depend*. 1983;11(1):105-109.
11. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013;346:f174.
12. Gupta R, Shah ND, Ross JS. The rising price of naloxone - risks to efforts to stem overdose deaths. *N Engl J Med*. 2016;375(23):2213-2215.
13. West NA, Severson SG, Green JL, Dart RC. Trends in abuse and misuse of prescription opioids among older adults. *Drug Alcohol Depend*. 2015;149:117-121.
14. Betz ME, Boudreaux ED. Managing suicidal patients in the emergency department. *Ann Emerg Med*. 2016;67(2):276-282.

15. D'Onofrio G, Chawarski MC, O'Connor PG, et al. Emergency department-initiated buprenorphine for opioid dependence with continuation in primary care: outcomes during and after intervention. *J Gen Intern Med.* 2017; 32(6):660-666.
16. Weiner SG, Baker O, Bemson D, Schuur JD. One-year mortality of opioid overdose victims who received naloxone by emergency medical services [abstract 402]. *Ann Emerg Med.* 2017; 70(4, suppl):S158.
17. DuPont RL, Compton WM, McLellan AT. Five-year recovery: a new standard for assessing effectiveness of substance use disorder treatment. *J Subst Abuse Treat.* 2015;58:1-5.
18. Merlo LJ, Campbell MD, Skipper GE, Shea CL, DuPont RL. Outcomes for physicians with opioid dependence treated without agonist pharmacotherapy in physician health programs. *J Subst Abuse Treat.* 2016;64:47-54.
19. DuPont RL, McLellan AT, White WL, Merlo LJ, Gold MS. Setting the standard for recovery: Physicians' Health Programs. *J Subst Abuse Treat.* 2009;36(2):159-171.
20. Humphreys K, Malenka RC, Knutson B, MacCoun RJ. Brains, environments, and policy responses to addiction. *Science.* 2017; 356(6344):1237-1238.
21. Williams AR, Bisaga A. From AIDS to opioids - how to combat an epidemic. *N Engl J Med.* 2016;375:813-815.