Annals of Internal Medicine

EDITORIAL

Being Explicit About Decisions: Prescribe Medications for Opioid Use Disorder on the Basis of Proven Effectiveness, Not Beliefs

Most of the more than 2.1 million persons with opioid use disorder (OUD) do not receive treatment (1, 2). Medical care for other chronic conditions often is fragmented and, in some cases, characterized by poor quality. However, few other conditions for which medical care is as poor or nonexistent are responsible for such a large number of deaths as OUD (49 000 from opioid overdose in the United States in 2017) (3).

Although some patients are not ready for treatment, major barriers to high-quality care are squarely in the realm of the health care delivery system. Again, unlike for other chronic conditions, access to 2 of the 3 medications approved by the U.S. Food and Drug Administration (FDA) for OUD—buprenorphine and methadone—is limited by regulations. Sublingual buprenorphine (often coformulated with naloxone) is an opioid partial agonist, and oral methadone is an opioid full agonist; both reduce illicit opioid use, opioid craving, and the risk for death (4). Prescribing requires special training outside postgraduate programs and either a "waiver" from the Drug Enforcement Administration (DEA) in the case of buprenorphine or treatment in a federally certified opioid treatment program in the case of methadone. Most physicians do not have a DEA waiver, and most who have one do not prescribe at all. Most addiction specialty treatment programs (>90%) do not have opioid treatment programs, which makes methadone treatment difficult to obtain (5).

Naltrexone has efficacy in reducing illicit opioid use and is not subject to such restrictive regulations. The extended-release injectable formulation is an opioid antagonist and requires an opioid-free detoxification period, typically 1 week, to avoid precipitating withdrawal. Despite this clinical challenge that many patients cannot surpass, early safety concerns regarding reduced tolerance and increased overdose risk, and the long-established evidence that buprenorphine and methadone are effective treatments for opioid addiction, extended-release naltrexone is favored in some institutions, addiction treatment programs, and patient support groups primarily because it is not an opioid (6).

In this context, whether patients receive any medication, as well as which medication they receive, seems to be determined less by efficacy and safety and more by regulatory policy and beliefs. Such personal or institutionally promulgated beliefs may be related to the meaning of abstinence and the effects of opioid agonist treatment. The American Society of Addiction Medicine defines *abstinence* as "intentional and consistent restraint from the pathological pursuit of reward and/or relief that involves the use of substances and other behaviors" (7). Patients, therefore, can be abstinent from illicit opioids while receiving treatment with buprenorphine or methadone. All 3 FDA-approved medications should be available to patients with OUD; if so, the key issue for clinicians (and patients) is how to choose among them.

Choice of medication for OUD should be guided by efficacy and safety and informed by cost-effectiveness. In their current *Annals* article, Murphy and colleagues (8) report a cost-effectiveness analysis of buprenorphine-naloxone versus extended-release naltrexone to prevent opioid use relapse. Their study, which followed well-established guidelines for conducting economic analyses alongside a clinical trial, is an eloquent demonstration of how cost-effectiveness analysis forces us to be explicit about the factors that influence our decisions. Clinician beliefs and preferences for or aversion to a particular form of treatment do not factor into the analysis.

From both the health care sector and societal perspectives, the authors noted higher 24- and 36-week intervention costs for extended-release naltrexone than for buprenorphine-naloxone. They also found small, nonsignificant differences favoring buprenorphine-naloxone at 24 and 36 weeks in both the economic (quality-adjusted life-year) and clinical (time abstinent from opioids) effectiveness measures between the 2 study groups. These results were robust to varied assumptions, specifically about medication costs. The authors concluded that buprenorphine-naloxone is most likely cost-effective compared with extended-release naltrexone. They also analyzed the per protocol results of the trial, which eliminated the challenges in initiating extended-release naltrexone treatment. Assuming that patients withdraw from opioids successfully (are opioid-free for 1 week and initiate naltrexone), then naltrexone may be cost-effective from the societal perspective. However, many persons do not complete withdrawal; thus, the per protocol analysis probably is less valuable for informing real-world settings.

In addition to the clinical trial on which Murphy and colleagues based their study, other evidence is mounting that buprenorphine-naloxone is more efficacious and safer than extended-release naltrexone in the real world. LaRochelle and colleagues (2) found that compared with no medication for OUD, buprenorphine-naloxone significantly lowered all-cause and opioid-related mortality after nonfatal overdose, whereas extended-release naltrexone did not. In another large claims database, patients were much more likely to discontinue extended-release naltrexone than buprenorphine-naloxone (9).

The clinical trial on which Murphy and colleagues based their research, as well as the cost-effectiveness analysis itself, demonstrated the challenges in initiating extended-release naltrexone therapy in persons with OUD, and the highlighted real-world studies demonstrated the difficulty in maintaining treatment in these

This article was published at Annals.org on 18 December 2018.

patients. By offering only naltrexone—a medication that most persons either will not receive or not continue—because of clinician or institutional beliefs, patients receive inferior treatment. In the context of a high mortality rate and already limited access to addiction care, we need to offer the best treatment that patients will, in fact, receive and continue.

Specific situations exist in which extended-release naltrexone may be the appropriate medication choice. Hadland and colleagues (10) demonstrated near-equal retention in care among adolescents receiving either buprenorphine-naloxone or extended-release naltrexone compared with behavioral treatment alone. In addition, extended-release naltrexone is FDA approved for alcohol use disorder; therefore, patients with both diagnoses may benefit from it over other medications. These are nuanced treatment decisions that should be made by considering individual circumstances.

We should evaluate treatment for opioid addiction as we do for other chronic medical diseases, by assessing efficacy, costs, risks, and the likelihood of success, and not on the basis of beliefs, which partly underlie regulations that restrict access. As with many other chronic disorders, OUD treatment comes in several forms and is often lifelong. Basing medical decisions on beliefs about medications does nothing to help the growing pool of those with OUD, who if untreated are likely to fall victim to an overdose.

Joshua A. Barocas, MD
Boston Medical Center
and Boston University School of Medicine
Boston, Massachusetts

Richard Saitz, MD, MPH
Boston University School of Public Health, Boston University School of Medicine, and Boston Medical Center
Boston, Massachusetts

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-3293.

Corresponding Author: Joshua A. Barocas, MD, Boston Medical Center, 801 Massachusetts Avenue, 2nd Floor, Boston, MA 02118; e-mail, joshua.barocas@bmc.org.

Current author addresses are available at Annals.org.

Ann Intern Med. 2019;170:127-128. doi:10.7326/M18-3293

References

1. **Substance Abuse and Mental Health Services Administration.** Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2018. HHS publication no. (SMA) 18-5068. (National Survey on Drug Use and Health. Series H-53).
2. **Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, et al.** Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. Ann Intern Med. 2018;169:137-145. [PMID: 29913516]
3. **National Institute on Drug Abuse.** Overdose death rates. 2018. Accessed at www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates on 31 October 2018.
4. **Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al.** Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017;357:j1550. [PMID: 28446428]
5. **Congressional Research Service.** Opioid treatment programs and related federal regulations. 2018. Accessed at https://fas.org/sgp/crs/misc/IF10219.pdf on 1 November 2018.
6. **Nunn A, Zaller N, Dickman S, Trimbur C, Nijhawan A, Rich JD.** Methadone and buprenorphine prescribing and referral practices in US prison systems: results from a nationwide survey. Drug Alcohol Depend. 2009;105:83-8. [PMID: 19625142]
7. **American Society of Addiction Medicine.** Terminology related to addiction, treatment, and recovery. Accessed at www.asam.org/docs/default-source/public-policy-statements/1-terminology-atr-7-135f81099472bc604ca5b7ff000030b21a.pdf?sfvrsn=0 on 1 November 2018.
8. **Murphy SM, McCollister KE, Leff JA, Yang X, Jeng PJ, Lee JD, et al.** Cost-effectiveness of buprenorphine-naloxone versus extended-release naltrexone to prevent opioid relapse. Ann Intern Med. 2019;170:90-8. doi:10.7326/M18-0227
9. **Morgan JR, Schackman BR, Leff JA, Linas BP, Walley AY.** Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. J Subst Abuse Treat. 2018;85:90-96. [PMID: 28733097]
10. **Hadland SE, Bagley SM, Rodean J, Silverstein M, Levy S, Larochelle MR, et al.** Receipt of timely addiction treatment and association of early medication treatment with retention in care among youths with opioid use disorder. JAMA Pediatr. 2018;172:1029-1037. [PMID: 30208470]