

## POLICY

# Medication development in opioid addiction: Meaningful clinical end points

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**The FDA's "abstinence" outcome measure for approval of new medications to treat opioid-use disorders has been difficult to achieve; developing and validating alternative meaningful outcomes could facilitate drug development.**

Opioid-use disorders have rapidly become one of the most challenging public health crises in the United States and around the world. In 2016, drug overdose fatalities claimed an estimated 64,026 lives in the United States, the majority of which resulted from prescription or illicit opioids (1). Opioids were also responsible for escalating annual hospital visits, a fourfold increase in neonatal abstinence syndrome, and an estimated doubling of the incidence of hepatitis C virus (HCV) infections, among other health consequences. The rising mortality and the extraordinary human toll and costs from opioid misuse and addiction, referred to as the "opioid crisis," are stimulating a vigorous response from federal agencies and private stakeholders.

As part of this response, developing new medications to reduce the burden caused by opioid-use disorders is a high priority. The U.S. Food and Drug Administration (FDA) has approved three medications to treat opioid-use disorders that improve outcomes including decreasing opioid use; reducing relapse, overdoses, and infectious disease transmission; and improving retention in treatment and psychosocial function, among other benefits. However, overcoming logistical and attitudinal barriers to the adoption of these medications remains a challenge, because only a small percentage of those who would benefit from these medications are treated with them. Also, whereas medications currently approved to treat opioid-use disorders improve outcomes, the relapse rates are still high, and not all patients respond. Thus, there is a pressing need to develop more effective and more easily used treatment alternatives (2). Unfortunately, the currently available tools and end points to evaluate and ultimately approve new medications to treat opioid-use disorders can act as

an impediment to medication development. These barriers must be addressed.

Like other substance-use disorders, addiction to opioids is a complex brain disorder involving alterations in the neuronal circuits underlying the ability to process reward, motivate actions, and regulate emotions and desires. Currently approved pharmacotherapies for opioid-use disorder reduce cravings and withdrawal symptoms by acting as agonists (methadone) or partial agonists (buprenorphine) at the mu opioid receptor. By contrast, the opioid antagonist medication (naltrexone) blocks the effects of misused opioids (for example, heroin, fentanyl, and prescription opioids). Both agonists and antagonists might also improve mood. At this point, no medication can undo the drug-induced changes to the brain that are involved in the relapsing nature of opioid-use disorder. Instead, the current goal of opioid-use disorder medications is to improve physical and psychosocial functioning to facilitate recovery. However, measuring these benefits during the course of a drug-development effort is challenging, in part due to the length of time and the large number of subjects that would be required to see meaningful differences in these distal outcomes. So instead, studies supporting registration of a new medication for opioid-use disorder have relied on showing that a larger proportion of patients on the study medication attain evidence of sustained cessation of drug use compared to those on a placebo. This end point, mistakenly believed to be a requirement for strict abstinence, was adopted because it is accepted that patients who discontinue use of substances accrue clinical benefit. For example, there is clear evidence that cessation of heroin use prevents overdoses and greatly reduces the risk of HIV or HCV infection.

Whereas achieving continuous abstinence is clinically beneficial, it is a high bar, one that is notoriously difficult to achieve (and sustain) for people in whom the brain circuits involved with self-regulation have been compromised by drug use (3). A high bar also deters the development of new agents to treat opioid addiction. This raises the question: Could patterns of opioid use other than sustained abstinence provide meaningful benefit to patients and therefore be appropriate as the basis for approval of new therapeutic agents for treating opioid-use disorder?

There is a precedent for regulators accepting outcomes other than abstinence end points. Harm from alcohol use has been linked to the degree of exposure, and there is strong evidence that reducing the quantity of alcohol consumed short of complete cessation is associated with improved health; thus, reduction of alcohol consumed to low-risk drinking patterns is a valid alternative to abstinence for clinical trials of drugs to treat alcohol use disorders. Facilitating use of quantity and frequency of alcohol consumption as a clinical outcome is the ability of patients to readily report these behaviors (4). Consequently, the FDA has accepted the percentage of subjects with no heavy drinking days (defined as less than 5 drinks/day for men and 4 drinks/day for women), not just abstinence, as an outcome measure in medication trials for alcohol-use disorder (5).

Less information is available on the benefits of reduced frequency or intensity of opioid use versus complete abstinence. McCann and colleagues (6) argue, however, that the risks associated with any episode of illicit drug use—including overdose, acquiring an illegal drug, and transmission of infection through needle sharing—mean that there may be important benefits from any reduction in the frequency of illicit drug use. Validating and then using new end points linked to reduced use in drug development requires evidence that reduced use (reductions in the amount

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or frequency in use) is associated with improved patient outcomes such as lower rates of fatalities, overdoses or infections, or other clinical benefits (7).

Studying the benefits and feasibility of end points reflecting decreased use, short of any periods of abstinence, for treatments for opioid-use disorder is complicated by the difficulties in quantifying the frequency or intensity of opioid use (8). Self-reports, as currently obtained, do not accurately measure actual drug use. Whereas frequency of use can be readily assessed, quantities are notoriously difficult to measure. For instance, differences in potency, purity, and dosage vary from purchase to purchase and impede accurate quantitation. Also, the opioid drug may contain other substances that can affect patterns of use and consequences; for example, heroin and counterfeit prescription opioids are frequently adulterated with fentanyl, leading to increased risk of overdose. Even when users report misusing prescription opioid drugs, they may purchase counterfeit drugs with unknown ingredients or may take the drugs in ways (snorting, injecting) that make quantitation problematic. In addition, when relying on blood or urine measures of drug exposure, the time course may be too short to capture all episodes of use or too long to capture changes in frequency. To address these challenges, we need to improve our ability to measure illicit opioid use, such as by developing biomarkers of exposure that are sufficiently sensitive to measure changes in both the quantity and frequency of drug consumption.

We are thus faced with three urgent challenges: determining how much reduction in drug use is clinically relevant, finding reliable and practical ways to measure such changes in drug use, and developing biomarkers predicting and indicative of response to new agents. To meet these challenges, we need studies of how to better measure quantity and frequency of drug consumption as well as clinical or epidemiological studies to determine how much of a change in quantity or frequency of opioid consumption is associated with meaningful health and functional outcomes. This will entail research on biomarkers of drug exposure, development of better self-report measures of quantity and frequency of drug use, and studies on the relationship

of changes in quantity and frequency to meaningful health outcomes.

Accepting that meaningful reductions in quantity and frequency of drug use may be associated with improvements in health is part of a broader recognition that empirically new approaches are needed to address the opioid crisis. For instance, FDA Commissioner Scott Gottlieb's recent testimony before the U.S. House Committee on Energy and Commerce about federal efforts to combat the opioid crisis reiterated the FDA's commitment to the development and use of new non-abstinence-based end points as part of product development (9). He also stated that the FDA will facilitate the development of new products that address a fuller range of the symptoms of addiction, including craving. Measures of social functioning (for example, employment and avoidance of incarceration) could also be explored as end points for benefits of reduction in use. In addition, the identification of outcomes that are meaningful to patients with an opioid-use disorder could inform the FDA about patient-focused drug development guidelines for opioid-use disorder medications. If these alternative end points could be used in drug development trials, this could attract pharmaceutical-sector investment because of enhanced trial feasibility, which could ultimately result in a wider range of effective medications to treat opioid-use disorders. It is important to emphasize, however, that seeking alternative efficacy outcomes is not an attempt to lower the standard of approval for medications to treat opioid-use disorders. Clearly, accepting alternative end points will be based on reliable and rigorous data that such outcomes provide meaningful benefits to patients and their families.

The opioid crisis and overdose epidemic gripping the United States make it imperative that we develop additional treatment options for opioid-use disorders in particular and substance-use disorders generally. Achieving a more nuanced understanding of how to achieve therapeutic benefit short of periods of abstinence will facilitate the development of new treatments. To achieve these transformative goals, the National Institutes of Health and the FDA are looking to actively support and partner with the academic community, with the pharmaceutical industry, and with patients

and their families (10). Together, we can develop the tools needed to bring effective addiction treatments to the growing population of patients who desperately need them.

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