New FDA Guidance on Endpoints for Demonstrating Effectiveness of Drugs for Treatment of Opioid Use Disorder

PEER REVIEWED

Use and abuse of opioid products has increased alarmingly over the last 20 years, along with deaths due to overdose. Now commonly referred to as the "opioid crisis", the number of opioid-involved overdose deaths in the US increased 90% from 2013 to 2017.[1] The first wave of this rising trend began in the 1990s, related to the increased prescribing of opioids. By 2010, the second wave of overdose deaths was largely due to heroin overdose, and in the past decade or third wave, heroin overdose deaths were replaced by synthetic opioids, namely illicit fentanyl. Nearly 70% of the 67,367 US overdose deaths in 2018 involved an opioid.[2] Each of these three overlapping waves has been associated with a different form of opioid, with a fourth possible wave predicted given the recent increase in the widespread use of cocaine and psychostimulants alongside opioids.[3] Although the US accounts for one-quarter of estimated drug-related deaths worldwide, similar trends have also been noted in Europe.[4]

Led by the US Dept of Health and Human Services (HHS) and in conjunction with its operating divisions including the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and the Substance Abuse and Mental Health Services (SAMHSA), a five-point Opioid Strategy was put in place in April 2017 to 1) improve patient access to addiction prevention and treatment, programs 2) improve availability of overdose-reversing drugs especially in high-risk populations, 3) strengthen public health data reporting, 4) support cutting-edge research advancing pain and additional treatments, and 5) advance the practice of pain management to enable access to high-quality, evidence-based pain care.[5] Similar initiatives in Europe have focused on reduction of public supply; improved prevention, treatment and rehabilitation programmes; decriminalisation; and provision of medications for opioid use disorder (MOUD).[4] The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) introduced important strategies to address overdose prevention in 2018 that included increasing awareness about overdose risk, providing effective drug treatments, and improving throughcare between prisons and communities. A second set of responses focus on the prevention of fatalities when overdoses occur.[6]

As part of the five-point Opioid Strategy to improve access to prevention and treatment in the US, FDA finalised a new policy in 2019 to encourage widespread innovation and development of new buprenorphine treatments for opioid use disorder (OUD) that may result in less misuse, abuse, or accidental exposure than previously marketed formulations.[7] The guidance details the types of studies the FDA recommends for buprenorphine depot products and includes considerations for trial design and recommended and novel efficacy endpoints related to buprenorphine.[8]

More recently (October 2020), the FDA released finalised guidance intended to help advance the development of new treatments for OUD, addressing the clinical endpoints acceptable for demonstrating effectiveness.[9] Historically, endpoints in clinical trials evaluating effectiveness of medications for OUD for purposes of FDA approval have generally used changes in drug use patterns as an endpoint; in this guidance, expansion of primary and secondary endpoints to include measures important to patients, their families, clinicians, and the public are encouraged.

Trials for treating OUD are typically randomised, blinded, controlled trials and can be either superiority or non-inferiority designs. For treatments intended for use as initial therapy, patients should be new to treatment and the trial should generally include a standard-of-care non-pharmacologic treatment. For prevention of relapse, patients already stable on other treatments for OUD should be studied and seen at frequent intervals, using an approved therapy as a comparator.[9] Newly-initiated patients are considered more difficult to treat than clinically stable patients, so substantial evidence supporting effectiveness in patients new to treatment would typically also support approval for treatments in clinically stable patients, but not vice versa.[9]

Reduction in drug-taking behaviour (drug use patterns) are most often used as an endpoint – the recommended primary efficacy endpoint is the proportion of responders, where "responder" is commonly pre-defined by abstinence or no detected or self-reported use during the specific assessment window, very frequently assessed and utilising both urine drug tests and self-report (a grace period may be incorporated). As with previous guidance on analgesic drug development, efficacy analyses should compare percentage of responders and include cumulative responder curves and graphic displays of individual patient responses.[10] Other endpoints that may be meaningful and should be considered as primary or secondary for inclusion in FDA-approved labelling include adverse outcomes of OUD, change in proportion of patients meeting DSM-V diagnostic criteria disease status (e.g., change from moderate or severe to remission at baseline to the end of the trial can be used as a primary or secondary efficacy endpoint), and other changes in drug use patterns (e.g., fewer usage per day or per occasion provided it can be measured and shown to predict clinical benefit).

Guidance asserts that reductions in adverse outcomes related to OUD continue to be desirable endpoints for study and encourages the use of various and novel adverse event-related outcomes such as overall or overdose mortality, need for emergency intervention, and hepatitis C virus infection/reinfection. Sponsors are free to propose other adverse outcomes as well and can even evaluate several adverse endpoints in the same trial, selecting one as the primary endpoint and one or more as secondary endpoints, or even combining outcomes in a composite or summary scale. Supportive data regarding baseline rates of the adverse outcomes would be required in determining sample size and trial duration estimates.[9]

Of note, guidance emphasises that very frequent measurements will provide more assurance of a substantial reduction in drug use, whereas infrequent drug use measurements result in greater uncertainty about the true magnitude of reduction in drug use. For this reason, absence of positive urine drug tests, absence of self-reported drug use, and attendance at frequent scheduled observations for these measures are components of a complete abstinence response definition; abstinence is no longer defined as no detected or self-reported use during a specific assessment time period.[9]

Guidance also permits the utilisation of drug use patterns other than abstinence to define clinical response to treatment, as long as sponsors specify how the change in drug use pattern will be created and measured as a priority, as these may be difficult to validate. For example, changes in drug use patterns such as *fewer occasions of use per day or reduced amount of use per occasion* are notoriously problematic to track with confidence and may/may not be associated with clinical benefit. Therefore, in addition sponsors should attempt to gather supportive data from longitudinal prospective observational studies as well as other real-world evidence to make the association that the reduction in drug use is associated with and even portends clinical benefit.[9]

Expectedly this new guidance promotes patient-reported outcomes (PROs) from both patients and family members for change in how patients feel or function (e.g., improvement in sleep or mood) by encouraging the development of new PROs on other domains to use as secondary outcomes, provided the magnitude of change in the trial representing clinical sustained benefit has been determined.[9] For example, the development of a fit-for-purpose valid outcome for measuring a reduction in the intensity of the urge to use opioids could serve as an important secondary endpoint in trials that utilise drug use patterns as a primary endpoint. Additionally, it would be important to determine how craving reductions correlate with sustained clinical benefit with the goal of determining how long reductions in craving need to be maintained in the trial setting in order to predict a sustained clinical benefit.

Finally, the collection of additional clinically meaningful outcome measures that may demonstrate clinical benefit of drugs for treating OUD, such as reduction in hospitalisations or improvements in the ability to resume work, school, or activities is also encouraged, even though these types of outcomes typically require large subject numbers and longer time periods than typical registration studies.[9] Guidance supports their inclusion even if not intended to support a regulatory decision, noting that these outcomes could provide the basis for inclusion in labelling. Importantly, *retention in treatment* as a stand-alone endpoint is not recommended, as various trial design features can promote incentives to remain in treatment even in the absence of meaningful clinical benefit. As always, if these types of novel endpoints are planned, guidance strongly encourages early discussion with regulators in the drug development process. Of course, regardless of the outcome measure(s) chosen for inclusion, the demonstrated clinical benefit of a product will be weighed against its risk of serious adverse events. In addition, if the product has abuse potential (which is the case with currently available MAT), FDA will further evaluate risk of diversion and potential risks to both patients and non-patients, particularly in children.

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