Methodological Issues in Design and Conduct of Opioid Use Disorders Studies

PEER REVIEWED

Opioid use disorders have significantly increased over the past decade, affecting between 26 and 36 million people worldwide. It is estimated that approximately 2 million people in the United States alone have substance use disorders related to prescription opioid pain relievers, with an additional 467,000 people having heroin use disorders[1]. Furthermore, there is accumulating evidence to suggest a link between the medically supervised use of prescription analgesics and heroin abuse. Efforts to make abuse deterrent formulas have not helped and to the contrary, an increase in heroin use was noted following the introduction of abuse deterrent formulations of prescription opioids such as OxyContin, with data suggesting that up to 70 % of those who stopped taking abuse deterrent formulation of OxyContin started to use heroin instead; very recent literature suggests a correlation between increasing heroin overdoses and a decreasing number of prescriptions for abuse-deterrent opioids and overdoses of same[2]. Of those who continued to abuse the abuse deterrent formulation, 43 % reported simply changing their preferred route of administration to the oral route, while 34 % reported being able to defeat the abuse deterrent mechanism and continued to inject or inhale the drug[3].

The large increase in the number of prescription opioid- and heroin-related overdoses and deaths has caused government agencies around the globe to launch various initiatives to stem the tide of growing opioid abuse. For example, the US Health and Human Services department has introduced several initiatives, including: increased education, guidance, updated prescriber guidelines to assist health professionals in making informed prescribing decisions, increased use of naloxone, and support of various programmes designed to expand the use of medication-assisted treatment (MAT) by combining medication and behavioural therapy[4]. The pharmaceutical industry has also responded to this growing epidemic by increasing its efforts to develop drugs to treat opioid use disorder. However, there is relatively little direction on the appropriate design and conduct of such studies. This short feature is an attempt to highlight important methodological and operational challenges that can arise in the conduct of such trials.

Typically, studies seeking to enroll subjects with opioid use disorders will permit male and female subjects 18 to 65 years of age who have a diagnosis of moderate to severe opioid use disorder according to DSM-5 criteria in the past 12 months, and who, importantly, are willing to switch to opioid substitution therapy. This motivation is a crucial feature, as adherence to medication, compliance with protocol procedures and the risk for diversion are all characteristic hallmarks of these subjects who often present with varying and unreliable social/medical histories. Therefore, diagnostic misclassification must be minimised. To this end, a full diagnostic interview or a DSM-5 checklist (at a minimum) should be required for study entry.

It is important to note that the DSM-5 does not separate the diagnoses of substance abuse and dependence as in DSM-IV TR. Rather, current criteria are provided for substance use disorder, accompanied by criteria for intoxication, withdrawal, substance/medication-induced disorders, and unspecified substance-induced disorders, where relevant. Otherwise the DSM-5 substance use disorder criteria are nearly identical to the DSM-IV TR substance abuse and dependence criteria, combined into a single list, with two exceptions: DSM-IV TR recurrent legal problems criterion for substance abuse has been deleted from DSM-5, and a new criterion for craving or a strong desire or urge to use a substance, has been added. The DSM-IV TR specifier for a physiological subtype has been eliminated in DSM-5, as has the DSM-IV TR diagnosis of poly-substance dependence.

Furthermore, the threshold for substance use disorder diagnosis in DSM-5 is set at two or more criteria, in contrast to a threshold of one or more criteria for a diagnosis of DSM-IV TR substance abuse and three or more for DSM-IV TR substance dependence. Finally, the severity of the DSM-5 substance use disorders is based on the number of criteria endorsed, with 2 to 3 criteria indicating a mild disorder; endorsement of 4 to 5 criteria indicating a moderate disorder; and 6 or more criteria indicating a severe disorder. Importantly, DSM-5 now defines early remission from a substance use disorder as at least three but less than 12 months without substance use disorder criteria (except craving), and sustained remission is defined as at least 12 months without criteria (except craving). Therefore, any outcome measures related to early and sustained remission should follow these criteria. Additional new DSM-5 specifiers include “in a controlled environment” and “on maintenance therapy” as the situation warrants.

There are two general types of study designs which can be done separately or combined when attempting to investigate drugs designed to treat opioid use disorders, classified as “induction” and “maintenance” designs. The goal of induction is to safely suppress opioid withdrawal as rapidly as possible with adequate doses of approved drugs such as Suboxone® (buprenorphine HCl/naloxone HCI dihydrate) or Subutex® (buprenorphine HCl), while the goal of maintenance is to prevent the emergence of withdrawal symptoms, suppress cravings, and attenuate the effect of self-administered opioids in subjects who continue to episodically use opioids.

When designing maintenance studies it is important to ensure that subjects be currently taking a stable, daily dose of an approved medication such as 8/2 to 32/8 mg buprenorphine/naloxone or Suboxone® tablets or films for at least 30 days prior to baseline and have positive buprenorphine and norbuprenorphine upon screening.

Subjects should not have received any medication such as methadone or buprenorphine for opioid dependence in the last 30-90 days and should have negative urine drug screening for these before randomisation. As such, subjects should demonstrate at least mild withdrawal symptoms as defined on a scale such as the clinical opioid withdrawal scale (COWS), with a score ≥ 9.

If induction is the main objective, or at least a formal part of the study, then subjects should have successfully undergone induction in the first three days and also be free from significant withdrawal symptoms and cravings for opioids, typically operationalised as ≤ 12 on the COWS at baseline, while also having a score of ≤ 20 mm on the 100-mm opioid craving visual analog scale (VAS) at baseline, in order to properly evaluate the maintenance response. The number of subjects who successfully complete induction, which can typically take between two and four days (with retention in treatment at day three serving as a primary outcome measure), serves as the key outcome measure for studies looking at induction. Other useful outcome measures for longer maintenance studies have included the following: craving VAS, SOWS/COWS, self-report of substance use, the addiction severity index – lite (ASI-Lite), a pain assessment NRS, the SF-36 v2, the work productivity and activity questionnaire – specific health problems (WPAI:SHP) and the clinician and patient global impression of change (C/PGI). Regardless of the nature of the study, it is essential that all reported medical history should be confirmed with urine/blood tests.

When conducting studies designed to assess the effectiveness of drugs designed to treat opioid use disorders, there are a number of unique operational challenges which need to be considered and resolved in order to help guarantee successful study outcome. The first concerns the qualifications of the investigator and staff to work in this indication. Although appropriate subjects can be recruited at most qualified sites with a psychiatry specialisation, it is imperative to ensure that the investigator is qualified to work with subjects suffering from opioid addiction specifically. The simplest way to do this is to require at least one member of the study staff (preferably the principal investigator) to be board certified in addiction medicine, and in the United States to have a Center for Substance Abuse Training (CSAT) waiver in place. This qualification signifies that the investigator is credentialled to work with opioid-addicted subjects, has previous experience with this subject population, and has likely undergone a minimum of eight hours of training by an accredited professional society (e.g., ASAM, AAAP, and AMA). Preferably, the investigator is in possession of this qualification prior to study start, however obtaining this certification could be made a condition of participation in the study.

The second challenge relates to the fact that many currently approved treatments for opioid addiction, can (at least partially) agonise the μ-opioid receptor and therefore have addictive properties of their own. Therefore study drug may be subject to abuse and/or diversion as well, which is defined as any use of study drug other than that for which it is intended. There are anecdotal reports of the "street" resale value for addiction treatments of $50 per tablet or more, making the easy availability of these treatments very attractive for those with access to resale channels.

There are a number of measures designed to help manage the potential for diversion by subjects and staff. Initially, this is through employment of a meticulous, tablet-by-tablet, drug accountability regimen at each site. It is only when the study drug is carefully tracked that it can be identified as missing in the first place. The second suggestion is to implement a study-wide drug diversion policy. The purpose of such a policy is multi-faceted. First, it should outline the minimum requirements at the site level for the storage, security and accountability of the study drug. Additionally, it should provide guidance as to potential signs of study-drug diversion (in subjects *and* in staff), including changes in appearance and/or behaviour, excessive absenteeism (from work and/or study visits) and a decrease in an individual's reliability. Finally, this policy should guide the sites as to the steps to be taken in case of suspected or confirmed study drug diversion, including, in the worst cases, reporting of the event to the authorities. All members of the site staff that come in contact with study drug should be required to read and acknowledge the policy by wet-ink signature, with the original filed in the study trial master file. In addition, and separate from the study, sites that handle such compounds as a matter of course should be encouraged to institute a zero-tolerance policy regarding theft of study drug or failure to report same.

A third operational challenge revolves around the recruitment of appropriate subjects for opioid use disorder studies. There are primarily two sub-groups of subjects in this indication; those who have become addicted to illicit opioids (heroin being the most prominent example) and those who have become addicted due to continued (prescription) use of opioid analgesics (e.g., opioids were originally prescribed for chronic or post-surgical pain). However, as noted earlier, many of these latter subjects often convert to illicit heroin use as well. From a clinical trials perspective, these two sub-groups represent very different populations; the former is easy to recruit, but less likely to comply with protocol procedures (and therefore more likely to miss critical urine testing procedures or drop out of the study) and importantly more likely to divert study drug. These subjects are more likely to be poly-substance abusers, with alcohol and sedative use disorder being common, and it is imperative that subjects do not meet criteria for other use disorders, with the exception of nicotine, prior to study participation. These subjects should not have any pending legal action that could affect compliance, such as house arrest or incarceration. The latter population are relatively more difficult to recruit, but typically are more motivated to quit their addiction and therefore comply with the protocol, remain in-study and follow study procedures. Significantly, in this latter population, subjects should have had an original diagnosis of chronic pain as the basis for them requiring prescription opioids for treatment initially, but should not currently have chronic pain requiring treatment. A mixture of urban/non-urban sites helps to ensure that subjects representing both sub-groups will be represented.

Regardless of the type of subjects, it is important to ensure that all subjects recruited to participate in the study are doing so with the correct motives, which should be thoroughly questioned prior to study participation. A first pass at assessing these motives, in addition to identifying those who may be prone to convert to illicit heroin use, can be attained through the use of a risk-assessment tool such as the screener and opioid assessment for patients with pain (SOAPP)® or the opioid risk tool (ORT). Subjects identified as being susceptible to such risks can be steered to avenues of treatment other than clinical research[5,6]. For similar reasons, advertising for the purposes of recruitment should be kept to a minimum. Ideally, the subjects recruited to participate (from either group noted above) should already be known to the investigator or staff, and be motivated to quit their dependency. Finally, it should be noted that in many CNS indications, the primary concern regarding subject recruitment is that it is variable, hard to predict, laborious and slow. However, due to the growing global prevalence of opioid dependence, a new concern regarding recruitment is that it occurs so quickly that it outpaces a site's and sponsor's/CRO's ability to manage it. Although it may sound enticing, swift recruitment that is ahead of projections can present numerous problems, including: a lag in the entry of data into the electronic data capture (EDC) system in use for the study, the accumulation of unmonitored data at the site, and the concern that the proper patients are not enrolled. In order to manage anticipated brisk enrolment at the study level, it may be necessary to impose controls on recruitment. One effective method is to mandate that each site "pause" enrolment activities at a preset ceiling (e.g., after five or six subjects), thereby giving sites the time to enter data, the monitors time to evaluate it, and the sponsor/CRO time to ensure that the optimal subjects are enrolled. Only when these have been confirmed, with no issues identified, should a site continue enrolment. In such an instance, there must be a commitment at the site to rapid data entry (i.e., within 48 hours) and by the monitor to be at the site as soon as possible after the "ceiling" subject is reached.

In summary, there are several unique methodological challenges in the design and conduct of studies assessing the efficacy of various opioid use disorder treatments. Nonetheless, with careful planning these can all be effectively managed. Trials and approvals of new and improved treatments for this growing epidemic are essential given the currently available treatment options and increasing global prevalence.

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