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Clinical Trial Design Challenges and Opportunities for Emerging Treatments for Opioid Use Disorder
A Review

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IMPORTANCE Novel treatments for opioid use disorder (OUD) are needed to address both the ongoing opioid epidemic and long-standing barriers to existing OUD treatments that target the endogenous μ-opioid receptor (MOR) system. The goal of this review is to highlight unique clinical trial design considerations for the study of emerging treatments for OUD that address targets beyond the MOR system. In November 2019, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the US Food and Drug Administration sponsored a meeting to discuss the current evidence regarding potential treatments for OUD, including cannabinoids, psychedelics, sedative-hypnotics, and immunotherapeutics, such as vaccines.

OBSERVATIONS Consensus recommendations are presented regarding the most critical elements of trial design for the evaluation of novel OUD treatments, such as: (1) stage of treatment that will be targeted (eg, seeking treatment, early abstinence/detoxification, long-term recovery); (2) role of treatment (adjunctive with or independent of existing OUD treatments); (3) primary outcomes informed by patient preferences that assess opioid use (including changes in patterns of use), treatment retention, and/or global functioning and quality of life; and (4) adverse events, including the potential for opioid-related relapse or overdose, especially if the patient is not simultaneously taking maintenance MOR agonist or antagonist medications.

CONCLUSIONS AND RELEVANCE Applying the recommendations provided here as well as considering input from people with lived experience in the design phase will accelerate the development, translation, and uptake of effective and safe therapeutics for individuals struggling with OUD.

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Opioid use disorder (OUD) is a major cause of disease burden, leading to increased pregnancy or birth complications, viral infections, and fatal overdoses.[1-3] The 3 effective and safe medications for treating OUD (MOUD) act through the μ-opioid receptor (MOR), the primary target for opioids misused for their rewarding effects.[4] The MOR agonists methadone or buprenorphine and the MOR antagonist naltrexone are the standard of care for OUD because they reduce risk of relapse, overdose deaths, infections, and criminal behavior,[5] but discontinuation and relapse still exceed 50% within 6 months.[6-8] Furthermore, each of these MOUDs have different induction and dosing procedures as well as regulatory, policy, and patient-level barriers that have hindered patient access and retention.[9] Thus, OUD treatment options need expansion through development of novel stand-alone therapies or adjuncts to existing MOR-based MOUDs.[10-12]

A critical step in developing novel treatments for OUD is the completion of randomized clinical trials (RCTs). However, the inherent features of OUD, including a pronounced physical dependence and a high risk of overdose, suggest the design of these trials will likely need to differ from designs used to evaluate existing treatments for OUD. There is not a strong consensus in the OUD field concerning standardized key trial design decisions or outcome measures. Given the importance of this topic and the need for new and novel OUD treatments, a meeting sponsored by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the US Food and Drug Administration

(FDA) was convened in November 2019 to discuss study design considerations unique to 4 candidate medication categories for OUD that do not directly target the MOR system: cannabinoids, psychedelics, sedative-hypnotics, and immunotherapeutics; a summary of highlights from the meeting has been previously published.[13] This article reviews the key trial considerations derived from that meeting and provides consensus considerations and recommendations for studies of non-MOR–based treatments for OUD.

Methods

The ACTTION Consortium for Addiction Research on Efficacy and Safety (CARES) meeting included participants from academia, government, and nonprofit organizations selected on the basis of their research, clinical, or administrative expertise relevant to the candidate medication categories or clinical trials of OUD treatments. There was no direct participation from any pharmaceutical company. Meeting details, including agenda, goals, list of attendees, presentations, and transcripts of discussion, are available on the CARES website.[14] The following considerations and recommendations were informed by the meeting presentations and discussions, literature reviews, and coauthors' feedback on iterative revisions of drafts of this article.

Discussion

Study Planning

Study planning should begin by specifying the stage in OUD treatment targeted by the intervention(s), as this decision will influence all subsequent design decisions. The core stages in the OUD treatment and recovery trajectory can be conceptualized as (1) current active use of opioids; (2) acute abstinence, nonmedically supervised withdrawal, and/or supervised medical withdrawal; (3) early recovery (eg, less than 6 months of abstinence with or without opioid agonist or antagonist treatment); and (4) sustained recovery (eg, abstinence from illicit opioid use for at least 6 months). Each stage has unique treatment needs, and study planning should consider whether the novel treatment will be adjunctive to existing regulatory agency-approved MOUD, which may be essential for those with physical dependence and withdrawal symptoms. The need for adjunctive treatment, including harm reduction strategies, such as naloxone training to prevent fatal overdose, would be essential for clinically unstable patients.

Historically, few OUD trials have incorporated the preferences of patients, and per patient-focused drug development,[15] we recommend using input from people with lived experience to guide the choice of primary and secondary outcomes. For instance, although treatment retention was found as the most reported outcome across 60 OUD trials, many patients report an eagerness to complete therapy and end agonist treatment as a main goal.[16] Strategies for incorporating patient perspectives into study planning include focus groups, interviews, online surveys, workshops, social media listening, and community-based participatory research strategies.[17,18] Guidance on methods for engaging patients and other relevant stakeholders are described elsewhere.[19]

Study Design

Intervention (Including Randomization, Blinding, and Dosing)

Trial designs will be dictated to a large extent by the stage of treatment that the intervention is targeting as well as the unique properties of the intervention under evaluation. The **Table** gives an overview of specific considerations for the 4 types of emerging medication treatments reviewed here.[20-54] The National Institute on Drug Abuse has identified additional emerging areas of interest for OUD treatment development that target a range of novel pharmacological mechanisms of action, such as respiratory stimulants, γ-aminobutyric acid metabotropic receptor family B agonists, and ghrelin antagonists.[11] Discussing all emerging treatments, including nonmedication interventions (eg, repetitive transcranial magnetic stimulation[55]), was beyond the scope of this meeting, yet many of the considerations and recommendations described here also apply to these other approaches. Each of these emerging treatments has specific characteristics that influence study design choices, including dosing, mode of administration, and timing of intervention relative to treatment stage.

For drug development, the criterion-standard efficacy and safety studies are double-blind, placebo-controlled RCT designs. However, for OUD, these designs face ethical concerns of a placebo-only condition and challenges in blinding treatment groups. Additional research designs that could be considered include adaptive or pragmatic trials and the use of real-world data as primary or secondary outcomes.[56,57] Regardless of the specifics of blinding and randomization, we recommend that efforts to examine novel compounds be paired with some form of standardized and efficacious psychosocial support, including in-person or digital treatment modules, to mitigate the risk that patients are left with no treatment if a compound fails.[58]

Comparators

The severe nature of the opioid physical dependence syndrome means that a placebo-controlled trial in the absence of an agonist MOUD might be unsafe or unfeasible for patients who are in early abstinence and at risk of opioid withdrawal symptoms, relapse, or overdose. Relevant alternative types of comparators include (1) low or subtherapeutic doses of study medication, (2) ascending doses of study medication, (3) standard-of-care pharmacologic or nonpharmacologic treatments in a comparative effectiveness trial design, or (4) a combination of different comparators.

The type of comparator will also influence whether the objective of the clinical trial is to test superiority or noninferiority between different treatment conditions. Investigators may choose to provide an MOUD as a platform therapy for all participants while comparing an active vs placebo adjunctive medication using a superiority trial design (eg, a sleep agent compared with placebo for those stabilized with methadone). Ethical concerns related to placebo dosing could also increase the appeal of noninferiority trials, although these are more complex in design and analysis than superiority trials, with challenges described elsewhere.[59]

Table. Unique Considerations Associated With 4 Emerging Treatments for Opioid Use Disorder

Consideration	Cannabis and cannabinoids	Psychedelics	Sedative-hypnotics	Immunotherapeutics (vaccines and monoclonal antibodies)
Rationale	The endocannabinoid and opioid systems interact with some subtypes of cannabinoid receptors that influence the rewarding effects of opioids. Some uncontrolled observational research has suggested that cannabis and cannabinoids can have a substitution effect on opioid use behavior.[20-27]	Classic psychedelics (serotonin 2A receptor agonists) have been associated with reduced substance use in naturalistic and clinical settings, with the strongest evidence for LSD as a treatment of alcoholism. Candidate psychological mechanisms of action include awe, cognitive flexibility, and insight; candidate biological mechanisms include inflammation and brain network functioning.[28-34]	Sleep is a basic biological system that can be affected by opioid use and can also affect the trajectory of opioid use. Sleep dysfunction is a common issue across all substance use disorders. Sleep disturbance can have profound effects on a patient's life, including ability to cope with craving, and can affect the cognitive effort associated with opioid abstinence.[35-41]	Active (vaccination) and passive (transfer of premade antibodies) immunization strategies rely on the presence of drug-specific antibodies to selectively bind to target opioids in plasma and prevent drugs from crossing the blood-brain barrier and reaching the brain. By reducing the concentration of free (unbound) opioids in the brain, vaccines and monoclonal antibodies reduce opioids' pharmacological effects.[42-50]
Types	Cannabis is a complex chemical entity that contains >100 botanically derived phytocannabinoids, each of which can be synthesized or isolated.	LSD, psilocybin (found in *Psilocybe* mushrooms), mescaline (found in peyote and other cacti), and dimethyltryptamine (found in ayahuasca).	Orexin-1 or 1/2 antagonists; tricyclics (Doxepin); antipsychotics (Quetiapine); melatonin; mirtazapine; or ramelteon. Benzodiazepines or benzodiazepinelike drugs (eg, Zolpidem) are often not used due to risk for misuse.	Individual and multivalent vaccines targeting specific types of opioids, including oxycodone, heroin, and fentanyl. Individual and multivalent monoclonal antibodies formulations against various opioids.
Example human trials (patients with OUD)	60 Participants with OUD were randomized to receive dronabinol, 30 mg/d, or placebo during inpatient supervised withdrawal followed by oral naltrexone induction and extended-release maintenance for 5 wk. Dronabinol reduced the severity of opioid withdrawal during acute withdrawal but had no effect on rates of extended-release naltrexone treatment induction and retention.[24]	74 Male parolees with a history of chronic heroin use participated in a 4- to 6-wk residential program involving preparatory therapy in conjunction with a single high-dose administration of LSD (300-450 µg) compared with treatment as usual (ie, outpatient weekly group therapy). The LSD treatment was well tolerated, and biologically verified continuous abstinence was significantly greater in the LSD condition than control condition.[51]	137 Participants receiving methadone for OUD who reported a PSQI score of ≥6 were randomized to trazodone, 50 mg, or placebo. They completed 2 night home polysomnography sessions that were separated by 1 mo. Trazadone did not significantly affect subjective sleep ratings or most objective sleep outcomes.[52]	347 Participants in Iran using morphine were injected with 3 doses of a morphine vaccine at baseline, 30 d, and 60 d. The concentration of antimorphine antibodies was correlated with number of morphine injections detected at 30 d, reaching their peak by 3 mo after first injections and did not return to baseline levels by 1 y.[53] An ongoing clinical trial of an oxycodone vaccine is currently being conducted in the US.[54]
Key challenges	Choice of study drug, including mode and route of administration, which is affected by product variation across states/countries; access to study drug and phase II or higher trials challenging because of schedule I status; clarity is needed around objective of intervention.	Preparation and therapeutic alliance between study participant and researchers is necessary to reduce psychological risks; active placebo might not be feasible and could be replaced using subtherapeutic doses of tested compound or an active control; access to study drug and phase II or higher trials challenging because of schedule I status.	Choice of study setting (and associated sleep technology) affects the quality of sleep measures; rapidly changing technology with different levels of comfort for participants; the effect on opioid use will depend on presence of acute or chronic sleep agent dosing as well as the treatment stage in which it is tested.	Potential for compensatory use of opioids; design vaccines and monoclonal antibodies that do not interfere with opioid agonists or antagonists or other critical medications; equally reduced rewarding effects of opioids as well as respiratory depressant effects.
Potential exclusion criteria	Current or previous dependence on or tolerance to cannabis or presence of alcohol or other substance use disorders or comorbid psychiatric disorders (eg, psychosis, anxiety).	Uncontrolled hypertension or comorbid psychiatric disorders (eg, bipolar or psychotic disorders); patients taking medications with perceptual effects or effects on serotonergic function.	Existing sleep difficulties or diagnosed sleep disorders that are not the primary target of the intervention (eg, severe central or obstructive sleep apnea) as well as alcohol or other substance use disorders; active use of illicit opioids as couse with some sedative-hypnotics may be life threatening.	Polyopioid use may require use of multivalent vaccines against multiple drug targets (eg, heroin/fentanyl). Potential need for using diagnostic assays or predictive biomarkers to select patients most suitable for vaccine treatment for comorbid immune-compromising diseases.
Outcomes and measures of interest unique to the intervention	Misuse risk, including subjective ratings of liking or wanting cannabis, cognitive performance.	Acute mystical/transcendent/awe experiences, meaningful/insightful nature of experience, life functioning, quality of life, affect, prosocial behavior, persisting adverse effects, including perceptual disturbance, cardiovascular outcomes (eg, heart rate, blood pressure), headaches, psychological distress, positive and negative effects on coocurring psychiatric disorders, risk for misuse, including use outside of controlled research settings.	Affect, opioid craving, objective and/or subjective measurement of sleep quality and sleep architecture measured using polysomnography, ambulatory monitors (eg, Sleep Profiler, which can be used at home and yield polysomnography-level outcomes), actigraphy (can be used as a primary or secondary measure of sleep by tracking movement, room lighting, etc.). Other wearable technology (eg, Oura Ring; Watchpat), ecological momentary assessment, consensus sleep diary, and retrospective questionnaires (eg, PSQI or Insomnia Severity Index).	Immunological and pharmacokinetic outcomes, including antibody response and the effect of antibodies on distribution of drug in plasma (vaccine efficacy in reducing the effects of clinically relevant doses of target drugs depends on the quantity and quality of the antibody response). Other measures include effect of vaccine or monoclonal antibodies on drug-liking behaviors.

Abbreviations: LSD, lysergic acid diethylamide; OUD, opioid use disorder; PSQI, Pittsburgh Sleep Quality Index.

Study Setting

RCTs of MOR-based MOUDs have been traditionally completed on an outpatient basis in settings, such as opioid treatment programs or medical offices, because of inherent restrictions on MOUD prescribing and dispensing. Some emerging treatments, such as sedative-hypnotics or vaccines, may have fewer regulatory or medical requirements compared with MOR-based treatments and therefore may afford more flexibility in the study designs and open opportunities for novel approaches.[60,61] Methods for remote data collection have advanced considerably during the SARS-CoV-2 pandemic, expanding possible approaches to collecting substance use outcomes (eg, remotely collected breathalyzer data for alcohol or tobacco use).[62-64] Recent parallel efforts to leverage nonspecialized care professionals to expand the OUD treatment infrastructure, including health care professionals,[65,66] may further bolster innovation. However, these approaches may not be useful in all cases; the study of some agents may require even more intensive in-person designs compared with traditional OUD clinical trials. The in-person interactions and monitoring required for safe delivery and evaluation of some novel treatments present challenges to conducting clinical trials on a larger scale, an issue the field has acknowledged and begun to address with more scalable intervention paradigms.[67,68]

Participant Characteristics

Participant selection in the form of inclusion and exclusion criteria are essential for ensuring that a trial targets the population of interest, minimizes variance in outcomes because of factors other than the intervention, and supports future meta-analyses. At minimum, we recommend that the following categories be addressed in the study inclusion and exclusion criteria and/or baseline data collection associated with the study: (1) opioid use variables, including historical (lifetime) and current (past year) opioid use behavior, including type, timing, amount, and route of administration of opioid(s), previous experience with opioid overdose, including hospitalization, OUD treatment history, and degree of OUD severity; (2) historical or current alcohol and other substance use disorders, including prior use of target medication; (3) medical history, including prescribed medications in past 90 days and concomitant medical and psychiatric conditions; and (4) psychosocial variables (eg, problems resulting from opioid use, including incarceration). In addition, basic patient demographic characteristics (eg, age, sex, gender, race and ethnicity, and socioeconomic status) should be collected with awareness of specific populations that are at risk of developing OUD or those who experience disparate consequences, including individuals with mental health disorders,[69] youth and young adults,[70] military veterans,[71] pregnant women,[72] racial and ethnic minority populations,[73,74] and individuals from particular geographic regions (eg, US Appalachian and Southern states).[75,76] Limitations should be considered when selecting eligibility criteria depending on specific safety considerations associated with the intervention under study.

Outcome Measures

The type of efficacy outcomes chosen for a trial depends on the goal of the trial (eg, targeted phase of OUD treatment, key comparators). Literature reviews have noted that primary and secondary outcomes and their associated measures vary widely across clinical trials for OUD.[16,77] Opioid abstinence and treatment retention have been the most common primary end points in clinical trials for OUD and other substance use disorders.[78] However, there is an evolving understanding of the importance of continuous measures of opioid use, including changes in use patterns, such as the frequency, duration, and amount of use.

The degree to which these different, but important, outcomes are clinically meaningful is still being debated.[1,16,79,80] Currently there are no criterion-standard outcomes in OUD trials. Thus, the below recommendations are meant to function as guideposts when choosing outcomes.

Primary Outcomes

The dichotomous outcome of opioid abstinence, defined as no detected or self-reported use within an assessment window, has been the most common measure of opioid use behavior in clinical trials.[78] According to the FDA Guidance for Industry regarding end points for demonstrating effectiveness of drugs for treatment of OUD,[78] drug use patterns other than abstinence can be used as thresholds to define treatment response. Measurement of such response-defining thresholds must be specified, and evidence from clinical trials, longitudinal observation studies, or other sources are needed to support the clinical benefit of a given drug use pattern (ie, reduction).[78] We recommend that both abstinence and patterns of opioid use be measured and that clear responder criteria be specified for each, with the potential for a grace period. For trials that identify opioid abstinence as the primary outcome, we recommend opioid use be assessed using objective (eg, urinalysis) and subjective (eg, patient, clinician, and/or observer) measures.[77] The field is currently moving to less frequent objective testing of these outcomes for practical reasons and to reduce the burden on participants. We recommend that decisions regarding frequency of testing be based on the clinical stability of the patient population, the pharmacological properties of treatment, and participation burden.

Trials of MOR-based treatments demonstrate that retention in treatment longer than 6 months is associated with better treatment outcomes compared with shorter durations of treatment or no treatment.[81] However, neither we nor the FDA[78] recommend that treatment retention be a stand-alone clinical end point, as retention can be easily influenced or driven by factors external to the intervention being examined. We recommend that at least 1 outcome consider general patient functioning as assessed through pre-post changes in *DSM* OUD diagnostic status or symptom criteria,[82,83] quality of life assessment tools, or other patient-centered outcomes that can better capture how a treatment is affecting a patient's life beyond acute opioid exposure.[79]

Secondary Outcomes

Key secondary outcomes, which could be primary outcomes depending on the aims of the study, include: (1) opioid withdrawal signs and symptoms; (2) opioid craving; (3) treatment adherence; (4) treatment satisfaction; (5) physical health (eg, comorbid diagnoses, including chronic pain); (6) mental health (eg, anxiety, depression, and other substance use); (7) cognitive and physical functioning (eg, memory, attention, sleep duration and quality, and pain severity); (8) personal and social functioning (eg, family and social relations, criminal behavior, employment, schooling, relationships, and

Box. Key Recommendations and Considerations

Study Objectives
- Prospective trial registration prior to the start data collection in publicly accessible database, including primary and secondary outcomes, hypotheses, and study objectives.
- Priority should be given to specifying the stage in OUD treatment that will be targeted with the intervention (eg, current active use of opioids, acute abstinence, nonmedically supervised withdrawal, and/or supervised withdrawal, early recovery, or long-term recovery) and determining whether the emerging treatment will be adjunctive to or independent of existing OUD treatments.

Clinical Trial Design
- Study design will ideally be double-blind randomized clinical trial.
- Comparators should include a placebo group (when ethically appropriate) and/or an active control comparison(s).
- If the novel treatment is a stand-alone intervention, then comparison should include an existing, evidence-based OUD treatment (eg, methadone, buprenorphine, naltrexone, or behavioral/psychosocial support).

Sample
- Participants should be a representative, diverse population of patients (ie, age, sex, sexual orientation, race and ethnicity, socioeconomic status, and history of substance use).
- Exclusion criteria that are too restrictive and may negatively affect the generalizability of the study should be carefully evaluated and included on the basis of safety or another enhanced rationale considered (eg, exclusion of participants with concurrent medical, physical, or mental health issues).

Primary End Point
- Primary outcomes should be chosen to align with the study objectives and the phase of treatment that is to be targeted (eg, symptoms of opioid withdrawal or craving will be more important to measure in early recovery rather than during long-term recovery). In addition, primary outcomes will need to be tailored to the expected treatment indication (eg, sleep measures for a sleep intervention).
- At minimum, we recommend that primary outcomes for trials beyond phase I include opioid use behavior, treatment retention, and at least 1 outcome that addresses global functioning (eg, change in *DSM* criteria, quality of life).
- A dichotomous measure to define responder (based on opioid abstinence or reduction in opioid use) should be a primary outcome, but also consider continuous measures of opioid use (ie, quantity, frequency).
- Selection of end points should be informed by input from patients and family members to determine the most salient OUD symptoms/experiences and outcomes.

Secondary Outcomes
- Potential secondary outcomes should include opioid withdrawal and/or craving, treatment adherence and satisfaction, physical and mental health, risk of misuse of study intervention, patient-focused outcomes, such as psychosocial functioning (including employment and legal issues), sleep, pain, and cognitive functioning, and health outcomes (eg, viral load if positive for HIV or hepatitis C virus).

Assessment of Harms
- Adverse events, including opioid-related adverse events (eg, hospitalization, naloxone administration, visits to emergency department), and reasons for premature terminations from trial should be collected and carefully reviewed with sensitivity to relapse risk and overdose.

Abbreviation: OUD, opioid use disorder.

housing and food stability); (9) health risk behavior (eg, hospitalizations, overdoses), and (10) risk of medication misuse (eg, rewarding or reinforcing effects of medication).

Risk and Adverse Events

A critical outcome in OUD trials includes opioid-related overdose or death, which is at increased risk during treatment initiation and the first several weeks after initiating abstinence or attempting opioid withdrawal.[84,85] We recommend that trials, especially early treatment trials, include frequent assessment of these opioid-related adverse events, which include hospitalization, naloxone administration, and emergency department visits. Trials should also include counseling on opioid overdose risk knowledge at the onset of enrollment (eg, Brief Opioid Overdose Knowledge tutorial[86] or the Overdose Education and Naloxone Distribution training) and provide naloxone.

Additional opioid-specific risks that might be monitored include infectious disease exposure and seroconversion rates (eg, HIV and hepatitis C). Emerging treatments may have unique adverse effects and events that should be monitored. For example, immunotherapeutics, such as vaccines and monoclonal antibodies specific for opioids, should be carefully evaluated for immune-related adverse effects in immunocompromised patients.[42] In contrast, some sedative-hypnotic medications and cannabinoids have risks, including acute psychiatric and/or physical health consequences, misuse risk, drug-drug interactions, and diversion that should be monitored.[87,88] Examples of potential risks of emerging treatments covered in the present review are included in the Table.

Challenges and Opportunities

Regulatory requirements and quality control issues, including variations in regulation at the regional and national levels in the US and other countries, can make large-scale clinical trials challenging. For example, cannabis (and other cannabinoids) and psilocybin (and other psychedelics) are all classified as schedule I drugs according to the Federal US Controlled Substances Act (ie, drugs with no currently accepted medical use and a high potential for misuse), making it more challenging and administratively burdensome to conduct clinical trials. Relatedly, both classes of drugs have a controversial history, including issues with social acceptance and legality.[89] Meanwhile, state-level regulation of cannabinoids has led to variable (if any) manufacturing standards across states, resulting in intervariations and intravariations in potency and dosing across cannabinoid products. This makes it difficult to generalize research findings across some marketed consumer products.

These challenges and perspectives are slowly changing, as evidenced by the recent FDA breakthrough therapy desig-

nation for psilocybin in the treatment of depression, and 3,4-methylenedioxymethamphetamine (MDMA) in the treatment of posttraumatic stress disorder.[90] In contrast, opioid vaccines are not designated as controlled substances by the US Drug Enforcement Administration (DEA), and therefore, DEA regulations would not complicate treatment per se. However, opioid conjugate vaccines consist of multiple components, including an opioid-based small molecule hapten, which could be regulated by the DEA as either a schedule I or II drug, thereby affecting research and manufacturing.[91] Manufacturing challenges related to DEA drug scheduling apply to a broad range of compounds currently in development, including synthetic cannabinoids, psychedelics, and nontraditional opioid receptor agonists and antagonists.

Another challenge is that the types of opioids being used has expanded from commercially produced opioids and heroin to also include fentanyl and/or its structural analogs, resulting in a dynamic opioid marketplace for which research may lag street-level use, type of drug, and availability. Recent data suggest increased exposure to fentanyl and its structural analogs across the US.[92,93] Opioids produce diverse effects on the development and nature of opioid physical dependence and withdrawal, and fentanyl appears to be engendering a unique and particularly severe withdrawal syndrome. Establishing a treatment's efficacy becomes especially challenging when the type of substance being targeted has such wide variability in terms of potency, route of administration, detectability, and potential for adverse outcomes.

A third challenge is that the complexity of OUD and its different stages of development are likely to have different (albeit overlapping) underlying mechanisms that require different types of or combinations of treatments.[11] For example, early sporadic use is a different stage in the life cycle from years of chronic, daily use. Furthermore, medication alone is often not a sufficient treatment for OUD, and it is important to include psychosocial and behavioral interventions and to tailor these nonpharmacological interventions to the stage of opioid use. There remain gaps in our understanding of how best to combine pharmacological and behavioral treatments.[58]

Despite these and other challenges, there are valuable opportunities for clinical trials with emerging treatments. Research methods are developing quickly, especially in sleep measurement, wearable devices for drug detection, remote data collection (eg, telehealth and wearable technology), and the development of genetic biomarkers for selection of phenotypes and endophenotypes that may better reflect underlying neurobiological mechanisms. The present review focused on study design considerations for clinical trials and did not discuss other relevant types of research, including preclinical studies, laboratory-based within-subject human studies, and observational/epidemiological studies.

Conclusions

The **Box** provides a summary of the key considerations and recommendations for clinical trials evaluating emerging non-MOR treatments for OUD. Promoting a unifying structure of best research practices as described in the present review will help the field build consensus as to the appropriate methodological strategies and prevent otherwise promising targets from languishing or being abandoned because of problematic study designs rather than true lack of efficacy or lack of uptake. In the context of a continually evolving and escalating opioid crisis, research must prioritize both innovation and efficiency. The field and the patients with whom we work will be best served by maintaining an open dialogue to develop a consistent methodological framework for the assessment and treatment of OUD.

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