REAGAN-UDALL FOUNDATION FOR THE FDA

A PRACTICAL RESEARCH AGENDA FOR TREATMENT DEVELOPMENT FOR STIMULANT USE DISORDER

Meeting Summary
May 2022



REAGAN-UDALL FOUNDATION for the Food and Drug Administration

A Practical Research Agenda for Treatment Development for Stimulant Use Disorder

Meeting Summary

Contents

Disclosure: This activity is one part of a multi-part Foundation project related to substance use disorder. The multi-part project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an overall award of $173,835 of federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA, NIDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

1. Introduction

The Reagan-Udall Foundation for the FDA, in collaboration with the U.S. Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), hosted a virtual public workshop on October 18, 2021 titled A Practical Research Agenda for Treatment Development for Stimulant Use Disorder: A Virtual Public Workshop.[*] During the workshop, experts examined the evidence for candidate endpoints and study design strategies for clinical trials of stimulant use disorder[†] treatments. Workshop speakers and participants represented federal agencies, health care providers, researchers, patients, caregivers, and payors. This document summarizes the discussion from the workshop. This document does not represent the official views of FDA or NIDA on stimulant use disorder research.

Background

Adverse outcomes specific to stimulant use and polysubstance use[‡] are a rapidly growing public health problem in the United States,[1] with the rates of overdose related to psychostimulants increasing since 2010.[2] More broadly, the National Center for Health Statistics recently found that drug overdose deaths in the U.S. have doubled since 2015.[3] While this increase was driven largely by synthetic opioids such as fentanyl and its analogs, 40% of deaths between 2019-2020[4] that involved illicitly manufactured fentanyl also involved stimulants. Although forms of behavioral therapy, such as contingency management,[5] have been shown to improve the outcomes for patients with stimulant use disorder, thus far no pharmacological treatments have proven to be effective for this disorder. Effective pharmacological treatments would offer patients additional treatment options and potentially further improve outcomes.

Although patient-reported outcomes can offer the most direct evidence regarding the treatment of certain conditions, there is disagreement about the validity of patient-reported outcomes in measuring the efficacy of treatments for stimulant use disorder.[6] Instead, abstinence has been the primary endpoint in most stimulant use disorder trials. However, short-term abstinence observed in a brief clinical trial does not necessarily predict long-term improvement in physical, psychological, or social functioning.[7] Furthermore, participants encompassing both patient and caregiver perspectives, emphasized that abstinence is not the only path to recovery; they seek improved quality of life such as housing, employment, transportation, financial security, education, interpersonal relationships, and health improvements. During the workshop, the participants discussed evidence supporting the association between improved functioning and novel endpoints, including changes in patterns of drug use and disorder status, as well as trial design considerations and strategies for increasing inclusivity and patient-centricity in trials.

[*] The agenda for the virtual public workshop on October 18, 2021 is provided in Appendix A.

[†] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines stimulant use disorder as "the continued use of amphetamine-type substances, cocaine, or other stimulants leading to clinically significant impairment or distress, from mild to severe."

[‡] Polysubstance use refers to use of more than one type of drug, such as a stimulant and an opioid.

2. Candidate Endpoints

To date, most clinical trials for stimulant use disorder treatments have used drug use patterns as the primary efficacy endpoint, measured by stimulant metabolites in patient urine over a specific period of time. Many of those studies have reported the number of patients achieving a period of no use (i.e., abstinence) as the indicator of treatment efficacy. This choice of endpoint may be driven by a perception that abstinence is a required endpoint for evaluation in clinical trials. However, both researchers and workshop participants from FDA emphasized that abstinence is not a requirement; rather, it is a trial endpoint that can be measured objectively and is correlated with the level of stimulant use. Additionally, absence of metabolites in urine is an intermediary measure of drug use rather than a treatment goal. A more appropriate goal may be to identify endpoints that are meaningful to patients, associated with long-term clinical benefit, and measurable in a clinical trial.

Challenges to Using Abstinence as a Treatment Outcome[7]

- It is a rare treatment outcome.
- It is difficult to achieve and may not represent trial participants' primary goal.
- It may not be a sensitive enough indicator of positive treatment response.
- It may be an initially unacceptable or unattainable goal for patients, which can cause it to be a barrier to patients participating in trials or entering treatment.

Brian Kiluk, PhD, Associate Professor of Psychiatry, Yale School of Medicine, shared work that examined the association between changes in the pattern of drug use and problem-free functioning (PFF)[§] and disorder severity. A panel of experts reacted to his presentation and provided their perspectives on what makes an endpoint meaningful.

In the discussion, speakers emphasized that meaningful endpoints in stimulant use disorder clinical trials should have the following characteristics:[6]

- Ascertainable during the trial timeline (i.e., able to demonstrate a clinical benefit within the trial period);
- Clinically meaningful and patient-centric;
- Formulated on evidence-based, prespecified thresholds; and
- Associated with measurable long-term benefit(s), such as PFF or reduction in adverse outcomes related to stimulant use.

Specific details of the session are described below.

2.1. Change in Patterns of Drug Use

Dr. Kiluk shared evidence for the use of change in patterns of drug use as a clinical outcome in trials for stimulant use disorder. He presented results from a meta-analysis using pooled data from seven research studies conducted to test treatments for cocaine addiction. The aim was to evaluate the relationship between cocaine use at the end of treatment with long-term functioning.

[§] Problem-free functioning is an "indicator of good functioning as defined by the absence of reported problems across the medical, employment, legal, family/social, and psychological domains on the Addiction Severity Index."[8]

In short, the researchers sought to identify a potential threshold of cocaine use that was associated with long-term functioning; and as such, a potential surrogate for clinical benefit. They found an association between fewer than four days of use in the last month of a treatment trial (in a 12-week trial) and meaningful improvement in problem-free functioning over 12 months post-trial.[8]

Dr. Kiluk also presented research by Roos et al. in which they looked at three cocaine use frequency levels at baseline and end of treatment: abstinence, low frequency (1-4 days/month), and high frequency (5+ days/month). They found a significant association between a reduction in frequency of use by at least one level and PFF at one year following treatment, even without post-trial pharmaceutical intervention.[9]

Dr. Kiluk continued to explain that changes in pattern of drug use must tie to a prespecified and validated threshold. From a statistical perspective, continuous measures of cocaine use demonstrate greater power for detecting associations with long-term cocaine use and functioning compared to categorical measures.[8,10] Although continuous measures are good predictors of long-term outcomes and offer trends based on the study population as a whole, they do not provide an indication of treatment response. Panelists proposed that prespecified thresholds for use (e.g., ≤4 days of use within one month) can be employed for a dichotomous "pass/fail" endpoint that researchers can interpret easily and be used to calculate the proportion of treatment responders.[11]

The panelists acknowledged that perspectives from patients, caregivers, and clinicians should inform the process for identifying meaningful research endpoints for stimulant use disorder. During the discussion, patient advocates shared that the frequency of use may not be as meaningful as improved functioning or overall health status. However, longer trials may be necessary to demonstrate improvement in functioning or health.

In the discussion, panelists agreed that stimulant use disorder trials could use the change in patterns of drug use as a meaningful clinical endpoint. However, researchers must prespecify a threshold of drug use that is based on and associated with a long-term clinical benefit, such as functioning. Dr. Kiluk and the panelists highlighted that changes in patterns of use can be defined and measured in a variety of ways. In addition, the components of an endpoint, including the assessment type, tool, and timing, must be validated as fit-for-purpose.

2.2. Change in Disorder Status Using Diagnostic Criteria

Another candidate endpoint discussed, change in disorder, can be measured various ways, including change in DSM-5 status (whether or not patients meet the criteria for diagnosis at the end of a study) or by change in DSM-5 severity category.[12] There are 11 DSM-5 criteria, which include strong desire to use; failure to fulfill obligations at work, school, or home; continued social or interpersonal problems; increased substance tolerance; and withdrawal symptoms, among others. Patients who exhibit two or more of the 11 criteria within a 12-month period meet the threshold for diagnosis. Stimulant use disorder is further categorized by severity depending on how many criteria a patient meets: two to three for mild use disorder, four to five criteria for moderate use disorder, and six or more for severe use disorder.

Panelists suggested that researchers could consider incorporating a binary indicator as a clinical endpoint based on whether patients meet the criteria for diagnosis at the end of the study. Because it is difficult to assess change in severity or identify that patients no longer meet diagnostic criteria in short-term trials, they also noted such an approach would necessitate an extended trial observation period.

The panelists noted that measures of change in disorder severity or remission rates have been used in treatment trials for psychiatric disorders (e.g., depression, anxiety, schizophrenia) as well as other substance use disorders. The group discussed examples for the use of change in disorder severity as a viable endpoint for clinical trials:

- In 2018, FDA released guidance, "Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment," that indicated a "sponsor could use the proportion of patients meeting DSM-5 criteria for remission of [opioid use disorder] at the end of the trial as a primary or secondary efficacy endpoint."[13]
- In previous research for alcohol use disorder, reduction in criteria count and severity category were associated with better outcomes at six-month follow-up.[14] In 2015, FDA released guidance, "Alcoholism: Developing Drugs for Treatment," that includes additional information about endpoint selection.[15]

Additional research is needed to understand how measures for other disorders and diseases can better chart stimulant use disorder.

Workshop participants discussed evidence from several studies that have found change in disorder severity to be a consistent indicator based on test-retest reliability and procedural validity, including evidence from other substance use disorders.[16,17,18] However, there are many known challenges to including existing diagnostic instruments, such as the Addiction Severity Index (ASI), in therapeutic trials due to their complicated scoring and lack of connection to current DSM-5 diagnostic criteria. Panelists also noted the burden on clinicians and patients when administering such instruments to assess disorder status: Only trained clinicians may administer the current diagnostic instruments through time-intensive, structured interviews.

The panel discussed additional evidence for the use of change in disorder severity from a study conducted by Silva et al. They assessed whether criteria count at the end of treatment was associated with follow-up outcomes and changes in diagnostic criteria from baseline to end-of-treatment in a study of computerized cognitive behavioral therapy (CBT) for substance use disorders.[**19] Silva et al. found a significant correlation between DSM-IV[††] criteria count and the ASI alcohol composite, which suggests that meeting a greater number of DSM-IV criteria is associated with greater alcohol problem severity. Conversely, no longer meeting the diagnostic threshold at the end of a six-month follow-up period was associated with greater abstinence and abated severity.

[**] The study included 83 patients who met DSM-IV criteria for substance dependence, including for marijuana, alcohol, and stimulants.

[††] The DSM-IV was the predecessor of DSM-5

The severity categorization in DSM-5 was added to create a more nuanced description, rather than a binary "yes/no" criteria for having a disorder. Additional research is needed on whether severity categorization correlates with clinical outcomes, which DSM-5 criteria are most important, and whether criteria should be prioritized or weighted. The group noted that defining disease severity by the number of DSM-5 criteria symptoms may mask improvements in the severity of individual symptoms. As such, a suitably designed, fit-for-purpose measure that incorporates both the number and severity of addiction symptoms could be useful as an endpoint in clinical trials.

3. Additional Considerations for Clinical Trial Design

Workshop participants discussed methods to improve the sensitivity of stimulant use disorder clinical trial designs to detect an effect. Patient advocates shared that initial and sustained engagement in trials is more compelling if target endpoints reflect their needs and preferences. Additionally, all participants recognized the need for clinical trials to better reflect the full spectrum of people who may benefit from treatment (e.g., pregnant persons, people of color, people who use more than one type of drug), while also acknowledging the trade-offs between a diverse sample population and potentially increased difficulty in finding effects. Finally, the group discussed ways to improve fidelity with trial protocols. These concepts are expanded upon below.

3.1 Strategies to Improve the Ability to Detect a Potential Treatment Effect

Known challenges that can hinder researchers' ability to detect a treatment effect in clinical trials include low rates of adherence to the investigational therapy, high rates of placebo response, heterogeneous trial populations, and low patient retention. Specific to stimulant use disorder, workshop participants suggested that researchers may consider leveraging adaptive trial designs to address a variety of sources of bias or error, including confounding and misclassification of exposure. For example, using the strategy of lead-in periods in adaptive trials can help address confounding by identifying participants who respond to a placebo; when unidentified, such participants can mask the effect of active treatment. Adaptive trial designs also can minimize misclassification of exposure by detecting participants who not likely to adhere to assigned therapy early in the trial. (Additional strategies for trial enrichment, including those to decrease variability, are described in FDA guidance from March 2019.[20])

3.2 Inclusion Criteria and Exclusion Criteria

There is an acknowledged need to expand who is included in clinical trials for stimulant use disorder. There is also inherent tension between including the most varied treatment population possible and avoiding provision of investigational treatment to patients who are not likely to benefit or who might be more likely to experience significant adverse events. If researchers create inclusion criteria that are too narrow, it can make recruitment more challenging, and they may miss an opportunity to understand a treatment's effects on particular subgroups; if inclusion criteria are too broad, studies may become inadequately powered for subgroup analyses.

For stimulant use disorder specifically, participants highlighted that expanding inclusion criteria can improve generalizability. Many patients with stimulant use disorder also have co-occurring mental health diagnoses. Including people with an Axis I psychiatric disorder who are engaged in care and stable on medication in trials is important because of the high rates of comorbidity with

stimulant use disorder. Additionally, the panelists discussed the need to include people with multiple drug dependencies when possible, given the high rates of polysubstance use. It may be easier to study these broader populations in later-stage trials, after the effect of the drug has been established in populations with fewer confounding conditions.

4. Future Research Considerations

Panelists agreed additional research is needed in various areas. First, they highlighted the need to understand better not only the patient trajectories for stimulant use disorder but also short-term and long-term outcomes for patients who receive treatment. Cohort studies may be valuable for understanding the long-term trajectories of patients with stimulant use disorder. Currently, NIDA supports research in adolescents through cohort studies like the HEALthy Brain and Child Development Study (HBCD) and the Adolescent Brain Cognitive Development Study (ABCD Study).

In addition, panelists noted the lessons learned during the COVID-19 pandemic about responding to urgent research needs and accelerating the use of innovative trial designs. These lessons could help inform other areas of research, including research for stimulant use disorder treatments. In May 2021, FDA released a guidance, "COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention," which included recommendations related to types of master protocols such as umbrella trials, platform trials, and basket trials.[21] These innovative trial designs can help maximize the amount of information collected in trials and increase research efficiency.

Further research is needed to understand how differences among patients – such as the route of drug administration (e.g., injection vs. snorting vs. smoking), the context of drug use, and the level and frequency of use – impact response to specific treatments. Tailoring the treatment to the population would improve the ability to detect a treatment effect in a trial. It seems unlikely that a single drug will be efficacious for all patients with stimulant use disorder; however, some drugs may work better in particular subpopulations. It is important that researchers recruit a trial population that allows for sub-analyses or provide a clear rationale for narrowing criteria to include particular groups, such as only patients who inject drugs or only patients who use drugs heavily.

Future research could also explore the optimal length for a trial, especially because stimulant use disorder is a chronic condition. It is important to balance the need for longer studies (e.g., studies longer than 12 weeks) to capture patient-relevant outcomes and considerations for patient burden and retention in trials. In most cases, the size and length of trials are limited by funding. Additional evidence is needed to understand the impact of longer trials on the ability to measure outcomes that are meaningful to patients, caregivers, and clinicians.

However, longer trial timelines require innovative approaches to keep patients engaged and to reduce the burden of trial participation. Incorporating technology to reduce patient burden while maintaining the necessary level of data collection and patient observation could be an option. For example, researchers could explore whether observed relationships between change in drug use patterns and PFF are robust with fewer face-to-face study appointments.

5. Conclusion

This public workshop hosted by the FDA Foundation in October 2021 brought together experts from the patient community, academia, clinical care, FDA, NIDA, pharmaceutical companies, and payers. (Agenda provided as Appendix A.) Those experts emphasized the need for continued investment in clinical research and for consensus around clinically meaningful and patient-centric endpoints for assessing treatments for stimulant use disorder. The discussions in October 2021 built on discussions from previous meetings on the topic of stimulant use disorder, including an FDA-convened Patient-Focused Drug Development meeting in October 2020, a Duke-Margolis meeting in December 2019, and an ACTTION meeting in March 2015.

Appendix A: Public Workshop Agenda

A Practical Research Agenda for Treatment Development for Stimulant Use Disorder

Virtual Public Workshop

Monday, October 18, 2021

12 – 5 p.m. ET

Event Description: The Reagan-Udall Foundation for the FDA, in collaboration with the U.S. Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), is hosting a virtual public workshop to discuss a practical research agenda toward treatment development for stimulant use disorder. Stimulant use disorder is defined in the DSM-5 as "the continued use of amphetamine-type substances, cocaine, or other stimulants leading to clinically significant impairment or distress, from mild to severe." Adverse outcomes related to stimulant use are a growing problem in the United States.[‡‡,§§] There are currently no effective pharmacological treatments for any type of stimulant use disorder. However, there are many opportunities to improve the study design of clinical trials for stimulant use disorder. Clinical trials that are more person-centered may result in increased sensitivity to detect a treatment effect, with the potential for such a treatment effect to be linked to more long-term outcomes that are meaningful both clinically and to the patient.[***] Meeting participants will respond to a proposed practical research agenda that focuses on innovation in clinical trial design and candidate endpoints for the evaluation of potential treatments for stimulant use disorder.

12 p.m. **Welcome**

- Susan Winckler, Reagan-Udall Foundation for the FDA

12:05 p.m. **Session 1: Efforts to Promote Treatment Development for Stimulant Use Disorder**

Presenters

- Janet Woodcock, U.S. Food and Drug Administration
- Nora Volkow, National Institute on Drug Abuse

12:45 p.m. **Session 2: Optimizing Clinical Trial Design for Stimulant Use Disorder**

Presenters

- David McCann, National Institute on Drug Abuse
- Madhukar Trivedi, UT Southwestern

[‡‡] Jones CM, Compton WM, Mustaquim D. Patterns and Characteristics of Methamphetamine Use Among Adults — United States, 2015–2018. MMWR Morb Mortal Wkly Rep 2020;69:317–323. DOI: http://dx.doi.org/10.15585/mmwr.mm6912a1

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Panelists

- Sarah Akerman, Alkermes
- Maria Sullivan, Pear Therapeutics
- Jessica Hulsey, Addiction Policy Forum
- Frances Levin, Columbia University
- Robert Walsh, National Institute on Drug Abuse
- Maryam Afshar, U.S. Food and Drug Administration

Discussion

2:15 p.m. **Break**

2:30 p.m. **Session 3: Identifying Clinically Meaningful and Patient-Centric Endpoints**

Presenters

- Brian Kiluk, Yale School of Medicine

Panelists

- Michelle Peavy, University of Washington
- Philip Rutherford, Faces and Voices of Recovery
- Deborah Hasin, Columbia University
- Ivan Montoya, National Institute on Drug Abuse
- David Reasner, U.S. Food and Drug Administration
- Celia Winchell, U.S. Food and Drug Administration

Discussion

4 p.m. **Session 4: Future Directions for Stimulant Use Disorder Research**

Panelists

- Marta Sokolowska, U.S. Food and Drug Administration
- Nora Volkow, National Institute on Drug Abuse
- Brandee Izquierdo, SAFE Project
- Denise Leclair, Novartis
- F. Gerald Moeller, Virginia Commonwealth University
- Pamela Scott, U.S. Food and Drug Administration
- Nicole Caffiero, Cigna

Discussion

5 p.m. **Adjournment**

This activity is one part of a multi-part Foundation project related to substance use disorder. The multi-part project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an overall award of $173,835 of federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

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