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What Defines a Clinically Meaningful Outcome in the Treatment of Substance Use Disorders: Reductions in Direct Consequences of Drug Use or Improvement in Overall Functioning?

Brian D. Kiluk[1], **Garrett M. Fitzmaurice**[2,3], **Eric C. Strain**[4], and **Roger D. Weiss**[2,5]

[1]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA

[2]Department of Psychiatry, Harvard Medical School, Boston, MA, USA

[3]Laboratory for Psychiatric Biostatistics, McLean Hospital, Belmont, MA, USA

[4]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[5]Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA

Abstract

Background—Sustained abstinence is currently the only accepted endpoint for pharmacotherapy trials for most substance use disorders (SUD), with the exception of alcohol. Despite recent efforts, the identification of a non-abstinence alternative as a clinically meaningful endpoint for drug use trials has been elusive.

Argument/Analysis—The current standard for establishing a clinically meaningful outcome in SUD trials is to demonstrate a reduction in drug use is associated with improvement in long-term functioning, yet data indicate relatively weak associations between drug use and various psychosocial problem domains. This may be because assessments most commonly used to measure an individual's functioning do not specify whether aspects of functioning are a direct consequence of drug use. The acceptance of a non-abstinence based endpoint for alcohol use disorder trials was supported in part through associations with reductions in alcohol-related consequences, yet measures designed to assess the direct consequences of drug use are rarely included in drug treatment efficacy trials.

Corresponding author: brian.kiluk@yale.edu.

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Conclusions—The field of substance use disorders should include measures of negative psychosocial and health consequences of drug use, as opposed to overall functioning, in the effort to establish meaningful non-abstinence based endpoints.

Keywords

Substance Use Disorders; Clinically Meaningful Outcome; Treatment Endpoint; Negative Consequences; Functioning; Addiction Severity Index; Inventory of Drug Use Consequences

INTRODUCTION

Regulatory agencies, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have traditionally evaluated and approved pharmacotherapies for substance use disorders based on their ability to promote abstinence. Although accepted clinical trial endpoints for the development of medications for treating alcohol use disorders were expanded to include reduction in the number of heavy drinking days (1, 2), there is no such equivalent for other substance use disorders (SUDs). The lack of a currently accepted outcome other than sustained abstinence as an indicator of treatment success may be a factor that has contributed to the shortage of approved pharmacotherapies for many SUDs (3). In response to the current opioid epidemic in the US, the FDA recently announced a strong interest in the development and use of novel, non-abstinence based endpoints to be included as part of product development, aiming to promote the development and approval of new addiction treatments (4). Yet the identification of an alternative to sustained abstinence as a clinically meaningful endpoint for clinical trials evaluating treatments for SUDs has been elusive. Researchers primarily focus on establishing the impact of pharmacological or behavioral interventions on reducing the frequency/quantity of drug use, either through self-report or biological evidence (e.g., urine toxicology), and there are many examples of efficacious interventions in this regard (5, 6). However, drug-taking behavior is considered merely a surrogate endpoint for demonstrating clinical benefit; for a non-abstinence based outcome measure to be deemed clinically meaningful, it should be capable of indicating change in how an individual feels and functions (7).

Efforts toward establishing a clinically meaningful treatment endpoint have focused on demonstrating an association between drug use outcome measures and indicators of long-term functioning (e.g., 8, 9, 10). While the general hypothesis for this line of work is that reductions in drug use achieved during treatment are associated with improvements in functioning in other areas, such an association is complicated by the distinction between whether the areas of functioning being measured are deemed direct or indirect consequences of drug use. Indeed, it is possible that some areas of poor functioning may not be related to drug use at all. This is a critically important distinction, yet has received relatively little attention in the search for a clinically meaningful treatment endpoint for SUD clinical trials. The purpose of this paper is to present a debate for the field: should we be measuring a *reduction in direct consequences of drug use* or *improvement in overall functioning* to establish a clinically meaningful, non-abstinence based outcome?

Relationship Between Drug Use and Functioning

Individuals with SUD often present to treatment with a myriad of problems across various life domains, including physical, psychological, and social functioning. These areas are generally deemed 'addiction-related' and are expected to be affected by successful treatment of the substance use itself. Yet, the connections between drug use and functional status in these life domains are quite complicated (11); empirical evidence over the past 30+ years supporting the assumption that abstinence from drug use results in improvement in these areas has been mixed (10, 12–15). A seminal paper published in 1981 by McLellan and colleagues (12) was one of the first to refute the notion of improvement in 'addiction-related' problems resulting from reductions in drug use, with comparatively weak correlations between drug use and medical, employment, and family problems (e.g., $r < .10$). There are several examples of SUD clinical trials reporting significant treatment differences with respect to reductions in drug use, yet without parallel differences with respect to reductions in psychosocial problem severity (16–21).

There may be several potential reasons for the lack of consistent findings. We argue that a primary reason is due to the measurement of functional status in these life domains, i.e., the severity of problems is being assessed in more general terms rather than as a direct consequence of drug use. For instance, the Addiction Severity Index (ASI) (22), a standard assessment instrument in virtually all clinical trials with drug-using populations, measures problem severity across seven domains of functioning (medical, legal, employment, drugs, alcohol, family/social, psychological). These domains are considered vitally important for understanding the reasons for seeking treatment, decision-making regarding the setting and content of treatment, and monitoring change in a patient's status. The ASI is an extremely useful instrument with sound psychometric properties, translated into over 20 languages, and available in the public domain (22). However, despite its benefits, the measurement of problem severity on the ASI does not distinguish among problems that directly *contribute* to substance use, those that *result* from substance use, those that *may contribute* to substance use and then are worsened by the use, and those that are *unrelated* to a person's use of a substance. A more nuanced conceptual framework for how life problems/functioning may or may not be related to substance use needs to be carefully considered when specifically assessing the potential benefits of reducing substance use.

For example, two items from the employment domain of the ASI ask: "*How many days have you experienced employment problems in the past 30?*" and "*How troubled or bothered have you been by these employment problems in the past 30 days?*" Note that both questions attempt to measure the quality of functioning in this domain without making any causal link between substance use and employment problems, and fail to distinguish between substance use-related employment problems, and employment problems that are not related to substance use. Greater problem severity (i.e., poor functioning), as determined by responses to the ASI, may not necessarily be substance-related. That is, general functional measures are influenced by many factors other than substance use and commonly used measures such as the ASI do not specifically ask if problems are drug-related.

This is not simply a problem for the ASI; it is often true for other measures of global functioning (e.g., quality of life) as well. For example, the WHOQOL-BREF (23), a

commonly used measure of quality of life, includes questions such as "*How would you rate your quality of life?*" and "*How satisfied are you with your health?*" Thus, it would seem an unrealistic expectation that a pharmacotherapy or behavioral therapy effective at reducing rates of drug use should also be required to demonstrate effectiveness toward reducing (or improving) problems in these areas that may not be directly related to drug use. Yet this is ultimately what the field of SUD treatment has been attempting to demonstrate in the search for a clinically meaningful endpoint (9, 24). If there are relatively weak associations between drug *abstinence* and problems in these overall life domains (e.g., 10), then why should we expect a *reduction* in drug use (short of abstinence) to be associated with reductions in problems?

Consequences versus Overall Functioning

An alternative to measuring improvement in overall functioning or reduction in problems would be to measure the direct consequences of drug use. Assessing the negative consequences of substance use is important to the evaluation process in both clinical and research settings. Moreover, it is worth emphasizing that diagnostic criteria for SUDs, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (25), require assessment of the consequences of substance use. A DSM-5 SUD diagnosis is largely based on a pathological pattern of behaviors directly related or attributed to use of the substance (e.g., spending a lot of time getting, using, or recovering *from use of the substance*; not managing to do what you should at work, home, or school *because of substance use*; giving up important social, occupational, or recreational activities *because of substance use*).

Despite its importance, there is no universally agreed upon measure of consequences relevant to multiple types of substance use disorders. One measure designed to assess consequences of alcohol and drug use is the Inventory of Drug Use Consequences (InDUC; 26), which was adapted from the Drinker Inventory of Consequences (DrInC; 27) to assess consequences of multiple drugs, rather than alcohol use alone. The InDUC contains 50 items, 45 of which measure consequences in five distinct domains: interpersonal, intrapersonal, physical, impulse control, and social responsibility. Unlike the ASI, items in the InDUC make explicit causal connections between problems and substance use. For example, two items (yes/no) from the social responsibility domain state: "*I have missed days of work or school because of my (drinking or) drug use*" and "*The quality of my work has suffered because of my (drinking or) drug use.*" In contrast to the two questions from the employment domain of the ASI highlighted earlier, these two items make causal (consequence) connections to substance use. The InDUC has subsequently been shortened to 15 items by selecting three items from each of the five domains; this brief instrument is known as the Short Inventory of Problems (SIP) for alcohol or drugs (28). The SIP, originally developed as a briefer version of the DrInC to measure consequences of drinking, has been modified to assess consequences related to any substance (alcohol or drug) use (28, 29) or drugs alone (30).

Although there are established and validated measures available, assessments of the adverse consequences of drug use have to date been infrequently used in clinical trials of SUDs. For

example, the National Institute on Drug Abuse (NIDA) Data Share web site (https://datashare.nida.nih.gov/) is an electronic environment that allows data from completed clinical trials to be distributed to investigators and the public. As of April 2018, the web site provides access to data from 63 completed studies; the majority of these studies were associated with either the NIDA Division of Therapeutics and Medical Consequences (DTMC) or the NIDA Clinical Trials Network (CTN). Of the 63 studies posted on the Data Share web site, 39 can be described as randomized clinical trials with substance use outcomes. Of these 39 trials, almost 80% (31/39) included the ASI as part of their study assessments. In contrast, only 10% (4/39) included a measure of consequences, the SIP, as part of their assessments.

The importance of measuring consequences of substance use is particularly relevant in light of the decision by the FDA and EMA to make an important shift in their evaluation of medications to treat alcohol use disorders, based on the relationship between a specific type of drinking reduction (i.e., absence of any heavy drinking days) and a corresponding reduction in alcohol-related negative consequences. Specifically, in a communication on "Clinical Trials for Drugs to Potentially Treat Alcohol" (https://www.fda.gov/Drugs/DrugSafety/ucm369499.htm), the FDA (2) states that "patients with alcohol use disorders can largely avoid the known consequences of drinking if they never have a heavy drinking day"; a "heavy drinking day" is defined as >4 standard drinks in a day for males and >3 drinks in a day for females. The alcohol field has long focused on the idea that drinking reduction could lead to an avoidance of negative consequences. For example, in two major multi-site studies in the US, Project MATCH (31) and the COMBINE trial (32), a "good clinical outcome" was defined by both drinking data and a measure of alcohol-related negative consequences (33). Importantly, a secondary analysis of COMBINE data (34) demonstrated that the absence of heavy drinking days was accompanied by few if any negative consequences. Because standard drink definitions and 'low risk drinking' limits vary worldwide (35), more recent efforts have evaluated reductions in World Health Organization (WHO) risk drinking levels as meaningful endpoints for alcohol treatment clinical trials (36–38).

It is unclear why measures of the adverse consequences of substance use are not more routinely included in the assessment battery for clinical trials of drug use disorders. One partial explanation is the focus on sustained abstinence as the only clinically meaningful endpoint for clinical trials (39). By definition, individuals reporting sustained abstinence must have no current adverse consequences of substance use (although they may currently be suffering from negative consequences incurred in the past). However, in the search for an alternative to sustained abstinence as a clinically meaningful endpoint, it becomes important to assess whether a reduction in drug use (short of abstinence) is associated with reductions in adverse consequences of substance use.

The idea of reduced use as a potential goal of treatment for alcohol and not for illicit drugs makes intuitive sense, as alcohol is legal. Also, because illicit drug use is deemed inherently 'risky' (based on unknown drug purity/presence of other toxic chemicals, and potential risky behaviors related to the act of using or obtaining the drug), there is likely no 'safe' level of use, as there is for a legal and regulated substance like alcohol. However, secular trends have

shifted, so that cannabis, formerly illegal throughout the United States, is now legal in much of the country. Moreover, many patients with opioid use disorders use legal prescription opioids. Therefore, the distinction between alcohol use disorders and drug use disorders on legal grounds has become blurred in some instances, highlighting the potential importance of examining the relationship between reductions in drug use and negative consequences. Furthermore, if use of illicit drugs is inherently risky, then reducing the frequency an individual engages in the behavior would seem to have some benefit (40).

Surprisingly, there are no known reports regarding a change in DSM diagnostic status following treatment (i.e., whether individuals continue to meet disorder threshold criteria) as an indicator of clinically meaningful improvement. This may be due in part to the relatively short duration of most clinical trials, in comparison to the 12-month timeframe required for meeting the criteria for sustained full remission in the former DSM-IV (41), which would have indicated clear evidence of improvement. It also may be reflective of researchers' preference for continuous outcome measures, rather than dichotomous or categorical outcomes, as they are generally known to have greater statistical power to detect a treatment effect (42). Nevertheless, the lack of inclusion of post-treatment/follow-up assessment of DSM diagnostic criteria in clinical trials is notable, despite its direct measurement of an individual's functioning with respect to drug-related problems or consequences. Although DSM-5 retained a categorical approach to indicate the presence or absence of SUDs, the addition of a tri-categorized severity scale (mild, moderate, severe) based on the number of criteria endorsed might provide a meaningful indicator of improvement with which to validate a non-abstinence endpoint.

The Trouble with Consequences

A number of problematic conceptual and measurement issues have been noted with respect to consequences in the definition and diagnosis of substance use disorders (43). In particular, substance-related psychosocial and health consequences are often multiply determined (i.e., highly dependent on a range of other variables), and the distinction regarding whether a consequence is due to substance use to any meaningful degree can be difficult (43). This distinction is even further complicated in the case of polysubstance use, such that it may be nearly impossible to determine which substance may be more/less responsible for a given consequence. Relatedly, measuring self-reported adverse consequences of substance use requires some level of insight on the part of the patient, and can be limited in those patients who are reluctant to acknowledge a causal link between problems and substance use; that is, an individual "in denial" may not accurately perceive the extent to which his/her drug use is problematic or inflicting harm. Although patient-reported outcomes are highly valued by the FDA when measuring a concept best known by the patient (44), the validity of patient-reported drug use, symptoms, and problems is often questioned in the field of drug use disorders (45).

Whereas biologic indicators of drug use (e.g., drug metabolites detected through urine testing) are commonly used to validate self-reported drug abstinence, as well as serve as primary efficacy endpoints, the use of biologic markers of adverse consequences of drug use has been relatively understudied with respect to establishing a clinically meaningful drug use

reduction endpoint. In other words, the identification of a drug use-specific biomarker of impaired functioning could be particularly valuable as a tool to validate the meaningfulness of a reduction in drug use. The identification of such a biomarker has been elusive, yet there have been promising findings in the recent literature regarding associations between cocaine abstinence/reduction and lowered endothelial dysfunction (46), for instance.

SUMMARY AND RECOMMENDATIONS

Abstinence from drug use and reduction in drug use (short of abstinence) have not been found to be strongly associated with improvements in functioning as measured by currently used, common instruments (e.g., the ASI). This may be due, at least in part, to the measurement of functional status. Specifically, measures of functioning do not distinguish whether problems are being assessed as a direct consequence of drug use or in more general terms that may often be unrelated to drug use. To date, studies of SUD treatment have only infrequently collected measures of adverse consequences of drug use in favor of more general measures of functioning. The goal of this paper is to propose and advocate that we should be measuring a reduction in direct consequences of drug use, rather than improvement in overall functioning, as a primary approach to establish a non-abstinence based, clinically meaningful outcome in SUD trials. This argument is not framed in terms of having to choose between measures of functioning and consequences; arguably, both should be measured in clinical trials, as both have value. However, given the evidence of a complex and relatively weak relationship with drug use, measures of general functioning are not recommended for evaluating the direct benefits of reductions in drug use.

In light of these points, we urge researchers and the field to further develop and apply measures of consequences in future trials of SUD treatment. It is unclear whether there is a sufficiently broad set of adverse consequences applicable across any type of drug (consistent with DSM-5 diagnostic criteria for SUDs), or whether there exist meaningful drug-specific consequences. Current instruments, such as the SIP, assess consequences as related to any type of drug use, with the potential to replace the words ‘drug use’ in each item with a specific type of drug (e.g., ‘because of my *cocaine use*’). This type of instrument is recommended for evaluating direct benefits of reductions in drug use, as it may be applied to polysubstance users or adapted for singular drug types. However, one can imagine certain adverse consequences that may be specific, and more common, to certain types of drugs than others (e.g., overdoses from opioids). Thus, developing and validating instruments that measure drug-specific consequences may provide a more sensitive tool to establish meaningful reductions. For example, a consequences scale specific to heroin use was recently developed using items that parallel DSM symptom checklists, with subscales representing unique domains of heroin consequences (47, 48). Given the inherent limitations of self-report, objective measures of drug use consequences, which include biomarkers (e.g., 49), should also be pursued with a focus on direct linkage to the diagnostic criteria for the disorder. The development and application of such measures will aid in the study of new treatments that may have efficacy, and will provide a more nuanced understanding of the relationships between substance use and functioning. Such work holds promise in aiding our study of SUD treatments, and ultimately in enhancing the clinical care of patients who suffer from these disorders.

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