Drug and Alcohol Dependence 158 (2016) 1–7

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Measures of outcome for stimulant trials: ACTTION recommendations and research agenda

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ARTICLE INFO

Article history:
Received 23 September 2015
Received in revised form 6 November 2015
Accepted 7 November 2015
Available online 21 November 2015

Keywords:
Stimulant use disorders
Outcome measures
Clinical trials

ABSTRACT

Background: The development and approval of an efficacious pharmacotherapy for stimulant use disorders has been limited by the lack of a meaningful indicator of treatment success, other than sustained abstinence.
Methods: In March, 2015, a meeting sponsored by Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) was convened to discuss the current state of the evidence regarding meaningful outcome measures in clinical trials for stimulant use disorders. Attendees included members of academia, funding and regulatory agencies, pharmaceutical companies, and healthcare organizations. The goal was to establish a research agenda for the development of a meaningful outcome measure that may be used as an endpoint in clinical trials for stimulant use disorders.
Results and conclusions: Based on guidelines for the selection of clinical trial endpoints, the lessons learned from prior addiction clinical trials, and the process that led to identification of a meaningful indicator of treatment success for alcohol use disorders, several recommendations for future research were generated. These include a focus on the validation of patient reported outcome measures of functioning, the exploration of patterns of stimulant abstinence that may be associated with physical and/or psychosocial benefits, the role of urine testing for validating self-reported measures of stimulant abstinence, and the operational definitions for reduction-based measures in terms of frequency rather than quantity of stimulant use. These recommendations may be useful for secondary analyses of clinical trial data, and in the design of future clinical trials that may help establish a meaningful indicator of treatment success.

Contents

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http://dx.doi.org/10.1016/j.drugalcdep.2015.11.004
0376-8716/

1. Introduction

Sustained abstinence is considered the only outcome currently accepted by the US Food and Drug Administration (FDA) as a valid endpoint for clinical trials evaluating pharmacotherapies for drug use disorders (FDA: Psychopharmacologic Drugs Advisory Committee, 2013; Winchell et al., 2012). However, this endpoint is often considered unrealistic, and the lack of meaningful alternative indicators of treatment success (Carroll et al., 2014; Donovan et al., 2012) may be one factor that has hindered the development and approval of an efficacious pharmacotherapy for stimulant use disorders (see Acri and Skolnick, 2013). On March 24th and 25th, 2015, a meeting sponsored by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION), a public-private partnership with the FDA, was convened to discuss 'Measures of Outcome for Stimulant Trials'. ACTTION's mission includes optimizing the design and execution of clinical trials to expedite the discovery and development of improved treatments. Participants were drawn from clinical investigators, representatives of the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the FDA, pharmaceutical companies, and healthcare organizations. The overall goal was to identify a research agenda for the development of outcome measures other than sustained abstinence that would be clinically meaningful and could be used as endpoints for stimulant use disorder clinical trials. The purpose of this review is to provide a summary of the state of knowledge regarding this topic area, as addressed at this meeting, and to make recommendations for the field moving forward.

2. Characteristics of a meaningful outcome measure

The FDA's Center for Drug Evaluation and Research (CDER) provides specific guidance to the research and pharmaceutical communities regarding the selection of endpoints for use in clinical trials. CDER has a formal qualification process for identifying specific measures that will aid in drug development, which include biomarkers and clinical outcome assessments (for more detailed information, see Qualification Process for Drug Development Tools, Center for Drug Evaluation and Research, 2014). In addition to the need for any assessment tool to have strong psychometric properties (e.g., reliability, validity), several aspects of the outcome measure should be considered for selection as an endpoint in stimulant trials and are discussed below.

Clinical outcome assessments are those that measure a patient's symptoms or level of functioning, and can provide both direct and indirect evidence of treatment response (depending on who is reporting the outcome: patient vs. clinician vs. observer). Of the various potential clinical outcome assessments possible, the FDA views patient-reported outcomes as the nearest to direct evidence for some conditions, as they come directly from the patient without interpretation from others. These are formally recommended "when measuring a concept best known by the patient or best measured from the patient perspective" (from FDA Guidance for Industry document: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims). Therefore, a patient-reported outcome may provide meaningful evidence of benefit from treatment for stimulant use, as the disorder is characterized by a wide variety of problems potentially better measured from the patient's perspective in some cases (more than mere frequency of drug consumption). However, in the treatment of stimulant use disorders, there is some disagreement regarding the validity of patient-reported drug use, drug-related symptoms and problems (Hjorthøj et al., 2012; Magura and Kang, 1996).

While most treatments (pharmacotherapy or behavioral) are designed to affect the target behavior of stimulant use, measuring rates of stimulant use may not be the sole indicator of treatment success. Treatment benefit is demonstrated by evidence of a positive impact on how an individual feels or functions in daily life; a meaningful outcome measure should be capable of indicating change in one of these areas. Although changes in biomarkers such as urine test results may be useful as an objective indicator of response to a therapeutic intervention, they are considered a surrogate (i.e., substitute) for how an individual feels or functions in their daily life, and may not be a particularly meaningful outcome of treatment for drug use disorders that are characterized by multiple physical and psychosocial problems/consequences (e.g., Winchell et al., 2012). Due to the chronic nature of stimulant use disorders, demonstrating significant change in physical and psychosocial domains is limited by the relatively short duration of most clinical trials. Therefore, a meaningful outcome measure would be a level of reduced drug use that is predictive of long-term improvement in an individual's functioning in these areas. Several clinical trials have documented a statistically significant reduction in urine measures of stimulant use; however, identification of the specific level of reduced stimulant use (in terms of duration of abstinence and/or reduction in frequency of use) that is associated with clinically meaningful indices of long-term improvement has not been established.

3. Challenges in measuring reductions in stimulant use

The existence of a valid, biological indicator for detecting stimulant use (i.e., urine testing) is a major advantage compared to other psychiatric disorders, yet also has important limitations as an outcome measure. In general, detection times for stimulant metabolites in urine are up to 2–3 days after the occurrence of drug use (Cone et al., 2003; Oyler et al., 2002; Preston et al., 2002), yet many additional factors result in substantial variability in the ability to detect urine metabolites (e.g., route of administration, dose/purity of drug, individual differences in drug metabolism, urine concentration, level of drug use chronicity). These factors often create wide variations in metabolite concentrations in urine (e.g., concentrations of benzoylecgonine, a cocaine metabolite, can be detected at 150 ng/mL but concentrations greater than