



## Review

# Toward empirical identification of a clinically meaningful indicator of treatment outcome: Features of candidate indicators and evaluation of sensitivity to treatment effects and relationship to one year follow up cocaine use outcomes



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## ABSTRACT

**Background:** Selection of an appropriate indicator of treatment response in clinical trials is complex, particularly for the various illicit drugs of abuse. Most widely used indicators have been selected based on expert group recommendation or convention rather than systematic empirical evaluation. Absence of an evidence-based, clinically meaningful index of treatment outcome hinders cross-study evaluations necessary for progress in addiction treatment science.

**Method:** Fifteen candidate indicators used in multiple clinical trials as well as some proposed recently are identified and discussed in terms of relative strengths and weaknesses (practicality, cost, verifiability, sensitivity to missing data). Using pooled data from five randomized controlled trials of cocaine dependence ( $N=434$ ), the indicators were compared in terms of sensitivity to the effects of treatment and relationship to cocaine use and general functioning during follow-up.

**Results:** Commonly used outcome measures (percent negative urine screens; percent days of abstinence) performed relatively well in that they were sensitive to the effects of the therapies evaluated. Others, including complete abstinence and reduction in frequency of use, were less sensitive to effects of specific therapies and were very weakly related to cocaine use or functioning during follow-up. Indicators more strongly related to cocaine use during follow-up were those that reflected achievement of sustained periods of abstinence, particularly at the end of treatment.

**Conclusions:** These analyses did not demonstrate overwhelming superiority of any single indicator, but did identify several that performed particularly poorly. Candidates for elimination included retention, complete abstinence, and indicators of reduced frequency of cocaine use.

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## 1. Introduction

### 1.1. Potential advantages of a commonly accepted outcome indicator

The field of treatment of illicit drug use has not yet achieved consensus on a practical, psychometrically sound, clinically significant, and broadly accepted indicator of treatment success or response (Donovan et al., 2012). In areas outside the addictions, identification and adoption of standard measures of treatment response and clinical significance has facilitated several important advances. These include the ability to more easily accrue and compare outcomes for treatments and trials in meta analyses, benchmark clinical research and clinical outcomes, set and monitor performance standards, compare outcomes among different subgroups and samples, clearly convey the magnitude of treatment effects to clinicians and policy makers, inform planning for equivalence trials, and facilitate comparisons against a common meaningful outcome standard. Moreover, adoption of common outcome measures to benchmark intervention trials does not constrain investigators for selecting additional outcomes theoretically linked to the treatments putative mechanisms of action.

The fields of alcohol and nicotine intervention research have made significant inroads in wider adoption of common outcome measures in clinical trials as well as moving toward defining benchmark indicators of treatment response. In nicotine research, prolonged abstinence and point-prevalence abstinence, with biochemical validation, are now standard measures for outcome trials (Hughes, 2007; Hughes et al., 2010; West et al., 2005). These measures have been subjected to extensive psychometric evaluation establishing reliability and validity, linked to multiple outcome domains, and shown to be sensitive to the effects of a range of behavioral and pharmacological therapies (Hughes et al., 2003, 2010).

For alcohol use disorders, percent days of abstinence and indices of heavy drinking (e.g., percent heavy drinking days) have become standard measures of outcome for treatment trials (Allen, 2003; Anton and Randall, 2005; Finney et al., 2003; Sobell et al., 2003).

These indices have been demonstrated to be associated with a range of drinking-related risks and consequences (Falk et al., 2010). Efforts have also focused on identifying clinically meaningful and reliable dichotomous measures of treatment success, or good clinical outcome (Anton et al., 2006; Cisler et al., 2005; Cisler and Zweben, 1999; Sobell et al., 2003). These have included rates of individuals who are completely abstinent, as well as rates of individuals with no heavy drinking days (Falk et al., 2010). Recognizing that many treatment effects take some time to emerge and the course of improvement is not always linear, some indicators include a 'grace period,' for example, by not including heavy drinking days that occur early in treatment or allowing a limited number of heavy drinking days during treatment in the dichotomous definition of good outcome (Falk et al., 2010; Winchell et al., 2012).

For illicit drug use disorders, a common definition of treatment response has been elusive, in part because of the complexity of determining what constitutes 'clinically significant' change (Winchell et al., 2012). Common conventions for evaluating clinical significance (Jacobson and Truax, 1991; Kendall et al., 1999; Kraemer et al., 2003b; Lambert and Bailey, 2012), such as normative comparisons or reliable change indices are not easily generalized to drug use disorders, e.g., because illicit drug use is essentially non-normative, definitions based on the concept of 'return to normative levels' generally imply full sustained abstinence. Although full abstinence is a relatively unambiguous positive outcome, limiting 'success' to complete abstinence may be an overly exclusive criterion, as the process of change is inherently dynamic and thus complete abstinence may not be an appropriate indicator of meaningful cessation behavior (Ciraulo et al., 2003; DeBusk et al., 1994; Hser et al., 2008; Hughes et al., 2010; Velicer and Prochaska, 2004). Moreover, given that brief slips are common, a dichotomous measure of prolonged abstinence may be a relatively insensitive measure in that (1) few individuals may meet this standard, and (2) individuals who use drugs once or twice would be considered treatment 'failures', even though they may have made considerable improvement with respect to individuals whose drug use is unimproved.

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