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Short communication

Generalizability of clinical trials for cannabis dependence to community samples☆,☆☆

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ABSTRACT

There is growing concern that results of tightly controlled clinical trials may not generalize to broader community samples. To assess the proportion of community dwelling adults with cannabis dependence who would have been eligible for a typical cannabis dependence treatment study, we applied a standard set of eligibility criteria commonly used in cannabis outcome studies to a large (N = 43,093) representative US adult sample interviewed face-to-face, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Approximately 80% of the community sample of adults with a diagnosis of cannabis dependence (N = 133) would be excluded from participating in clinical trials by one or more of the common eligibility criteria. Individual study criteria excluded from 0% to 41.0% of the community sample. Legal problems, other illicit drug use disorders, and current use of fewer than 5 joints/week excluded the largest percentage of individuals. These results extend to cannabis dependence concerns that typical clinical trials likely exclude most community dwelling adults with the disorder. The results also support the notion that clinical trials tend to recruit highly selective samples, rather than adults who are representative of typical patients. Clinical trials should carefully evaluate the effects of eligibility criteria on the generalizability of their results. Even in efficacy trials, stringent exclusionary criteria could limit the representativeness of study results.

1. Introduction

Concerns have emerged as to whether results from tightly controlled trials, generalize to patients commonly seen in community settings (Blanco et al., 2008a; Braslow et al., 2005; Humphreys and Weisner, 2000; Institute of Medicine, 1998; Spall et al., 2007). It has been suggested that some exclusion criteria in clinical trials are overly restrictive, provide little additional patient safety or internal validity (Humphreys et al., 2005; Humphreys and Weisner, 2000; Spall et al., 2007), and severely limit the generalizability of study results. The National Institute on Drug Abuse has consistently stressed the need to increase the generalizability of clinical trials (National Institute on Drug Abuse, 2009a,b,c).

Cannabis use disorders which include cannabis abuse and dependence are the most common drug use disorders in the US, and their prevalence has been growing over the last decade (Compton et al., 2004). Clinical trials of interventions to treat these disorders usually include several exclusion criteria which may yield highly selective study samples (Denis et al., 2006). Furthermore, few clinical trials on cannabis dependence are available (McRae et al., 2003). Consequently, the generalizability of results from cannabis dependence studies has not received much attention, but remains important in interpreting the results of these studies as well as studies that will be published in the future.

It is not known whether samples of clinical trials for cannabis dependence represent adults with these disorders in the community. The goal of this study was to assess to what extent to which eligibility criteria commonly used in cannabis dependence clinical trials would likely exclude adults with cannabis dependence

☆ A supplementary data table is available with the online version of this article. See Appendix A.
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from the general population. To examine the extent to which general population would be represented in cannabis dependence treatment studies, we apply commonly used clinical trial eligibility criteria to all individuals with a current diagnosis of cannabis dependence in a large national sample. By applying this method to the population of individuals with cannabis dependence regardless of their current treatment status, we seek to assess the possible effects on a large proportion of individuals with the disorder.

2. Methods

2.1. Source of data

Data were drawn from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). The 2001–2002 NESARC is a nationally representative sample of the adult population of the United States conducted by the National Institute on Alcoholism and Alcohol Abuse (NIAAA) that has been described in detail elsewhere (Grant et al., 2003a,b, 2004a,b). The target population was the civilian noninstitutionalized population, 18 years and older, residing in households and group quarters in the United States. Face-to-face interviews were conducted with 43,093 respondents. The survey response rate was 81%. Blacks, Hispanics, and young adults (ages 18–24 years) were oversampled with data adjusted for oversampling and nonresponse. The weighted data were then adjusted to represent the US civilian population based on the 2000 census. DSM-IV cannabis dependence was assessed with the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule—DSM-IV Version (AUDADIS-IV) (Grant and Hasin, 2001), a fully structured diagnostic interview for non-clinician interviewers. The high reliability and validity of the AUDADIS cannabis dependence diagnosis ($\kappa = 0.70–0.94$) has been demonstrated in numerous clinical and general population studies in the US and abroad (Canino et al., 1999; Chatterji et al., 1997; Cottler et al., 1997; Grant, 1995; Hasin et al., 1997; Ustün et al., 1997). Clinical reappraisal studies showed good concordance between DSM-IV AUDADIS diagnoses of cannabis use disorders including cannabis dependence and those of psychiatrists (Canino et al., 1999; Cottler et al., 1997).

2.2. Study selection

To locate studies, we conducted electronic database literature searches, examined the reference sections of research reports, reviews, book chapters, and consulted authors working in this area. We searched the Cochrane Database and found two reviews, one on psychotherapeutic interventions for cannabis use and dependence in outpatient settings (Denis et al., 2006) and another on cannabis and schizophrenia (Rathbone et al., 2008). We searched the Pubmed database using the following phrase: [canna* OR marijuana* OR marihuana*] AND [dependence] AND ["treatment" OR "intervention"]. Inclusion criteria focused on studies that: (1) used an intervention for cannabis dependence; (2) enrolled participants 18 years or older; and (3) had DSM-IV or ICD-10 definitions of cannabis dependence. Two authors (MO and SSK) independently screened the titles and abstracts of all publications obtained by the search strategy. All potentially eligible studies were assessed independently for inclusion by two authors with disagreements adjudicated by the senior author (CB). We considered all social, psychotherapeutic, and pharmacological interventions for cannabis dependence regardless of model, setting, duration of intervention or country where the study was conducted. We then summarized the most commonly used exclusion criteria reported in these studies (Table 1).

We note that research groups in the US and outside of the US have published treatment studies on individuals with problematic cannabis use (Copeland et al., 2001; Martin and Copeland, 2008; McCambridge et al., 2008). These studies were not considered in our study as their samples included individuals under the age of 18 (Dennis et al., 2004; McCambridge et al., 2008), or did not use DSM-IV diagnoses of cannabis dependence (Copeland et al., 2001). However, most exclusion criteria for these studies resembled those of treatment studies we considered (e.g. literacy, heavy alcohol use and other illicit drug use) (Copeland et al., 2001; Martin and Copeland, 2008).

Although focused on cannabis use and other substance use disorders, other studies have included individuals with schizophrenia, psychotic disorders, and depression (Bonsack et al., 2007; Edwards et al., 2006; Findling et al., 2009; Kay-Lambkin et al., 2009; Rathbone et al., 2008). This important and developing line of research was not considered because the trials did not assess cannabis dependence, focused on other substance use disorders, or included individuals under age 18 year (Findling et al., 2009; Kay-Lambkin et al., 2009), though some used exclusion criteria included in our study (e.g. lack of literacy).

2.3. Clinical trials exclusion criteria

Some eligibility criteria for cannabis outcome studies parallel those used in alcohol outcome studies and thus were operationalized following previous conventions (Blanco et al., 2008b). These criteria include concurrent treatment, medical conditions, illicit drug abuse or dependence on other drugs, social instability, lack of reliable transportation, insufficient education/literacy, and legal problems previously described in other areas of substance use such as having legal proceedings or having felony assault history (Humphreys et al., 2005). Concurrent treatment included treatment in an alcohol or drug detoxification rehabilitation program, inpatient ward of psychiatric or general hospital, outpatient clinic, drug or alcohol rehabilitation program, methadone maintenance program, or treatment by a mental health professional during the past 12 months. Medical conditions often excluded from trials included hypertension, heart and liver disease, and pregnancy. Illicit drug abuse or dependence to other drugs was assessed with the modules on substance use disorders (SUD).

To help facilitate tracking participants for follow-up assessment, trials often exclude socially unstable patients. Respondents were considered socially unstable if they were unemployed, not in school, and unmarried at the time of the survey. Subjects were considered to lack reliable transportation if, when asked about reasons for not seeking treatment, they stated that they did not have any way to get clinical research site. Subjects were also often considered to have insufficient English literacy if, when asked about reasons for not seeking treatment, they stated that they did not go because of concerns over English literacy. Subjects were also classified as having an insufficient level of education if they had not completed at least the sixth grade. Legal problems were operationalized as having been arrested, having been held at a police station, or having had any other legal problems because of their drinking, medicine or drug use in the past 12 months.

Subjects were classified as suicidal if they reported having suicidal ideation in the previous 12 months. Several cannabis dependence treatment studies also excluded persons who were assessed as having "severe psychiatric distress." Since some of the studies define this criterion as having a psychotic disorder, subjects were classified as ineligible if they had been told by a mental health professional or by any physician that they had schizophrenia or other psychotic disorder. An alternative operationalization of "severe psychiatric distress" included meeting criteria for bipolar I, II, or major depressive disorder during the past 12 months. Using at fewer than 5 joints per week in the previous month was assessed with questions on the frequency of use available in the NESARC. Since most of the survey respondents reported using 1 joint per occasion, the criterion was operationalized as reporting using cannabis less than nearly every day in the previous month. Information on whether the respondents were referred or mandated to treatment was not available in the NESARC and could not be operationalized.

To guard against the possibility of variations in the results due to differences in definitions, we tested different algorithms for defining the eligibility criteria. For instance, we also conducted the analyses including 12-step program attendance in "concurrent treatment" and applying "using less than 40 days in the last 90 days" instead of at least 5 joints/week previous month, and "dependence on other drugs or alcohol" instead of "illicit drug abuse or dependence" as described in some large cannabis outcome studies (Stephens et al., 2002; The Marijuana Treatment Project Research Group, 2004).

We also conducted supplementary analyses on the probability of meeting an additional exclusion criterion by individual criteria. We further determined the

Table 1
Estimated percentage of adults with current cannabis dependence (past 12 months) in the NESARC excluded from typical clinical trials of treatments for cannabis dependence by traditional eligibility criteria.

Efficacy eligibility criteria (past 12 months)	Current (past 12 months) cannabis dependence ($N = 133$)	
	%	95% CI
Suicidality	15.98	(4.96–40.96)
Psychotic disorder	2.59	(0.26–21.4)
Concurrent treatment (all "professional" treatment)	14.81	(4.80–37.48)
Medical conditions or pregnancy (HTN, heart disease, liver disease, pregnancy)	16.64	(4.84–43.95)
Using fewer than 5 joints/week in the previous month	37.44	(17.92–62.12)
Illicit drug abuse or dependence (except nicotine and caffeine)	38.22	(19.68–60.97)
Inability to provide contact (unemployed and unmarried and NOT student)	2.03	(0.20–17.73)
Lack of reliable transportation, excessive commuting distance	2.67	(0.16–31.97)
Lack of English literacy	0.00	(0.00–0.00)
Lack of sufficient education/literacy (less than sixth grade)	0.00	(0.00–0.00)
Legal problems (incarceration, legal problems interfering with treatment)	40.96	(22.92–61.80)
Referred/mandated treatment	NA	
Overall percentage	80.03	(55.77–92.72)