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Generalizability of clinical trials for alcohol dependence to community samples

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Abstract

There is a growing concern that results of tightly controlled clinical trials of individuals with alcohol use disorders may not generalize to broader community samples. To assess the proportion of community-dwelling adults with alcohol dependence who would have been eligible for a typical alcohol dependence treatment study, we developed a new, simple method: we applied a standard set of eligibility criteria commonly used in alcohol 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). We found that approximately one-half (50.5%) of all individuals with a DSM-IV diagnosis of alcohol dependence (n = 1484) and 79.4% of those who sought treatment (n = 185) were excluded by one or more study criteria. Individual study criteria excluded from 0.9% to 48.2% of the overall sample and 0.8% to 43.7% of the treatment-seeking sample. For the overall sample, the lack of motivation/compliance and financial situation criteria excluded the largest percentage of individuals. In the treatment-seeking subsample, comorbid medical conditions and legal problems excluded the largest proportions of individuals. Our study provides a new method to assess the generalizability of clinical trials, and gives further evidence that typical clinical trials for alcohol dependence likely exclude most adults with the disorder in the community and under care, and support the notion that clinical trials recruit “pure” rather than “typical” patients. Clinical trials should carefully evaluate the effects of the selected eligibility criteria on the generalizability of their results.

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Conflicts of interest

Dr. Blanco has received research support from Somaxon, Pfizer and GlaxoSmithKline. Dr. Olfson has received grants from Bristol-Myers Squibb, AstraZeneca, and Eli Lilly and Company, has worked as a consultant for Bristol-Myers Squibb, Eli Lilly and Company, Pfizer, and McNeil, and serves on a speaker’s bureau for Janssen. Dr. Nunes has previously served on the Cephalon/Alkermes, Inc. speakers’ bureau and advisory board. Drs. Okuda and Hasin and Ms. Liu report no competing interests.

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Keywords

Generalizability; Alcohol dependence; Clinical trials; Eligibility criteria; Inclusion criteria; Exclusion criteria

1. Introduction

In designing clinical trials for alcohol use disorders, investigators must grapple with the clinical complexities of individuals with these disorders (Carroll, 1997; Moyer et al., 2002). Adults with alcohol dependence are a highly heterogeneous group; a substantial proportion present with significant psychiatric and somatic comorbidity (Hasin et al., 2007; Mannelli and Pae, 2007). However, patients with a variety of psychiatric and general medical comorbidities are often excluded from trials designed to test new treatments. Applying widely used eligibility criteria to two samples of patients whose outcomes were known, a recent study found that eligibility criteria resulted in moderate to very large bias in outcome estimates and that, contrary to expectation, it did not increase statistical power (Humphreys et al., in press).

As with other areas of psychiatric treatment research (Rabinowitz et al., 2003; Westen and Morrison, 2001), exclusion criteria are used extensively in alcohol treatment studies to optimize internal validity, protect patient safety, and enhance likelihood of treatment success (Humphreys et al., 2005; Peele, 1998). Restrictive eligibility criteria, however, are not always well justified (Spall et al., 2007). As a result, concerns have emerged regarding whether results from tightly controlled trials generalize to patients with complex clinical presentations that are common in community settings (Humphreys and Weisner, 2000; Institute of Medicine, 1998; Velasquez et al., 2000). For example, as compared with enrolled participants, individuals excluded from clinical trials of alcohol dependence have a greater likelihood of being African-American, having a low income, and having more severe alcohol, drug, and psychiatric problems (Humphreys et al., 2007; Humphreys and Weisner, 2000). As a result, the treatment effects achieved by clinicians in community settings may fall below the results of clinical trials, which could lead to decreased reliance of evidence-based practices.

The generalizability of clinical trials for alcohol dependence has been estimated mainly from samples of patients entering care. For instance, Humphreys and colleagues assessed the generalizability of alcohol treatment outcome studies by applying a set of commonly used eligibility criteria to a small treatment-seeking sample (Humphreys and Weisner, 2000) and to cases drawn from different alcohol treatment systems (Humphreys et al., 2007). Many patients in those systems would not have been able to participate in clinical trials using common eligibility criteria. A limitation of this important observation is that it cannot be safely extrapolated to the adult U.S. population with dependence. From the standpoint of public policy, it is important to move beyond local treatment-seeking samples to general population samples that more broadly represent individuals in need of treatment. The greater the proportion of individuals in need of treatment for alcohol dependence who qualify for a trial, the more the study results will generalize to the population in need.

We assess the extent to which common eligibility criteria from alcohol dependence clinical trials would likely exclude adults with alcohol dependence from a large national sample, the National Epidemiological Survey for Alcohol and Related Conditions (NESARC). This approach provides a new method to estimate the population generalizability of clinical trials. The NESARC is the largest epidemiological study conducted to date in the United States to include measures of a broad range of Axis I and II psychiatric disorders, including the full

range of alcohol use disorders. We apply common clinical trial eligibility criteria to all individuals with a current diagnosis of alcohol dependence and to the subsample of individuals treated in the past year in order to examine the extent to which these populations would have been represented in alcohol treatment studies, and examine the limitations of the generalizability of alcohol dependence studies.

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., 2003b, 2004). 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. Field methods included extensive home study and structured inperson training, supervision, and quality control, including random call-backs to respondents to verify data, are described in detail elsewhere (Grant et al., 2005, 2006, 2003b, 2004).

Diagnoses were made according to the criteria of the DSM-IV using the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV), a fully structured diagnostic interview designed for experienced interviewers who are not clinicians (Grant et al., 2003a). The reliability of the AUDADIS-IV alcohol diagnoses is documented in clinical and general population samples (Chatterji et al., 1997; Grant et al., 2003a; Hasin et al., 1997a) with test retest reliability ranging from good to excellent (κ = 0.70–0.84). Convergent, discriminant, and construct validity of AUDADIS-IV alcohol use disorder criteria and diagnoses were good to excellent (Hasin and Paykin, 1999; Hasin et al., 1990, 1994, 2003, 1997c), including in the World Health Organization/National Institutes of Health International Study on Reliability and Validity (Cottler et al., 1997; Hasin et al., 1997b; Nelson et al., 1999; Pull et al., 1997; Ustun et al., 1997; Vrasti et al., 1998), where clinical reappraisals documented good validity of *DSM-IV* alcohol use disorder diagnoses (κ = 0.60–0.76) (Canino et al., 1999; Cottler et al., 1997; Hasin et al., 1997b; Nelson et al., 1999; Pull et al., 1997; Ustun et al., 1997; Vrasti et al., 1998).

All potential NESARC respondents were informed in writing about the nature of the survey, the statistical uses of the survey data, the voluntary aspect of their participation, and the federal laws providing strict confidentiality of the identifiable survey information. Those respondents consenting to participate were interviewed after receiving this information. The research protocol, including informed consent procedures, received full ethical review and approval from the U.S. Census Bureau and the U.S. Office of Management and Budget.

2.2. Clinical trials exclusion criteria

We based our main analyses on the exclusion criteria summarized by Monahan and Finney (1996) and studied by Humphreys et al. (2005). This summary gathered information from 701 alcohol treatment outcome studies (conducted between 1970 and 1998) and identified the most frequently used set of criteria in clinical trials of treatments for alcohol dependence (Table 1). Included studies focused on an intervention for alcohol use disorders, enrolled participants 18 years or older, had five or more participants in each treatment condition,

assessed at least one drinking-related outcome variable, and were published in English. To examine the robustness of our results, we also examined the data applying alternative operationalizations of these criteria used in other trials (Humphreys et al., 2005), including some recent large clinical trials that have use less restrictive criteria (Project MATCH Research Group, 1997; The COMBINE Study Research Group, 2003).

For the presence of comorbid psychiatric conditions, 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. Concurrent alcohol treatment included treatment in an alcohol or drug detoxification rehabilitation program, inpatient ward of psychiatric or general hospital, outpatient clinic, or treatment by a mental health professional (a psychologist, social worker, psychiatrist, or another physician) during the past 12-months. Medical conditions included hypertension, heart and liver disease, and pregnancy. Nearly one-third of alcohol treatment studies explicitly excluded subjects who were expected to have low compliance or to have lack of motivation for treatment, as subjectively assessed by the study investigators (Humphreys et al., 2005). For the purposes of this study, subjects were classified as noncompliant or lacking motivation if they responded negatively to a series of queries about perceived need for treatment (e.g., “my family thought I should go but I didn’t think it was necessary”, “I wanted to keep drinking”). Residence was considered to be distant from the treatment facility if, when asked about reasons for not seeking treatment, the subject stated that they did not have any way to get to the clinic. Consistent with commonly used criteria in clinical trials (Humphreys et al., 2005; Monahan and Finney, 1996), subjects were classified as having insufficient education/literacy if they had not completed at least the 6th grade. A history of legal problems was 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. Since the NESARC only included respondents 18 and older, we assessed exclusion due to age by estimating the proportion of respondents who were 65 and older.

Survey respondents were deemed ineligible to participate in clinical trials due to their financial situation if they reported that they wanted to go to treatment but insurance did not cover it or that they could not afford treatment. As a way to ensure assistance in tracking the participant for follow-up assessment, trials often exclude socially isolated patients (socially unstable) (Humphreys et al., 2005). Respondents were considered socially unstable if they were unemployed (and were not students) and unmarried at the time of the survey. Information on neurocognitive problems and residential stability was not available in the NESARC and could not be operationalized.

2.3. Analysis plan

We first determined the percent (and 95% confidence intervals) of survey respondents that would be excluded by individually applying each criterion of the clinical trials. Because individuals might have been excluded by more than one criterion, we also calculated the overall percentage of subjects that would have been excluded by the simultaneous application of all of the measurable criteria. We conducted these analyses for all individuals with a current DSM-IV diagnosis of alcohol dependence (n = 1484), and for the subsample of individuals who sought treatment (n = 185) in the past 12 months. For the latter, noncompliance/lack of motivation, distance from the treatment facility and financial/insurance barriers were not assessed, since these were asked when assessing reasons for not seeking treatment, and therefore by definition, had not prevented subjects from seeking treatment. Similarly, for obvious reasons, concurrent alcohol treatment was not considered an exclusion criterion in the treatment-seeking subsample.

The NESARC weighs each observation to correct for their complex sampling design, including differential probabilities of selection and nonresponse. We report percentages based on these weighted estimates. We used the SUDAAN statistical software package (Research Triangle Institute, 2004) to accommodate the sampling design and weights of the surveys to calculate percentages and corresponding 95% confidence intervals.

3. Results

The percentage of subjects excluded by at least one criterion was 50.5% among respondents who met DSM-IV criteria for alcohol dependence, and 79.4% of those who sought and received treatment in the past year. The percentage of respondents excluded due to the application of a single criterion ranged from 0.9% (age > 65) to 48.2% (noncompliance/lack of motivation) in the overall sample of respondents with alcohol dependence, and 0.8% (age > 65) to 43.7% (medical conditions) among those seeking treatment (Table 1). For the overall sample, noncompliance/lack of motivation for treatment, and financial situation were the two criteria with the highest percentage of individuals. For the treatment-seeking sample, medical conditions and legal problems were the criteria comprising the greatest percentage of individuals who would not be eligible. The presence of illicit drug abuse or dependence also excluded a notable proportion of individuals in both samples.

Application of these criteria using the operationalizations applied in other trials (Humphreys et al., 2005; Project MATCH Research Group, 1997; The COMBINE Study Research Group, 2003) did not result in exclusion of a lower percentage of subjects. For example, when the criterion “psychotic disorder” was broadened to “presence of a psychiatric/emotional disorder” (major depressive disorder, bipolar disorder, dysthymic disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, and psychotic disorder), exclusion due to psychiatric comorbidity increased from 1.9% to 27.1% of subjects in the overall sample, and from 10.6% to 43.2% in the treatment-seeking subsample. This change resulted in 60.5% and 86.0%, respectively, being excluded by one or more criteria. By contrast, operationalizing “illicit drug abuse/dependence” as abuse or dependence of any illicit drug except cannabis, a criterion used in several clinical trials including MATCH (Project MATCH Research Group, 1997) and COMBINE (The COMBINE Study Research Group, 2003), or requiring 8th grade rather than 6th grade education resulted in no changes in the proportion excluded from the overall or treatment groups.

4. Discussion

Consistent with previous research (Humphreys et al., 2007; Humphreys and Weisner, 2000), the results of this study suggest that traditional criteria for clinical trials of alcohol dependence lead to the exclusion of a high percentage of individuals. Previous research has shown that clinical trials tend to exclude from participation approximately one-half of their screened subjects, although in some samples single criteria lead to more extensive exclusions (Humphreys and Weisner, 2000; Moncrieff and Drummond, 1998). By using community, rather than only treatment-seeking samples, our approach extends prior work by providing a new method to assess the population generalizability of clinical trials. We assessed the impact of alternate sets of eligibility criteria and estimated their effects on individuals who meet diagnostic criteria for the disorder in the community and in the subsample who seek treatment.

The results bolster concerns that clinical trials for alcohol use disorders recruit “pure”, rather than “typical” patients (Marlatt, 1999). Approximately one-half of the individuals with alcohol dependence in the general population would be excluded by widely used eligibility

criteria and some designs would be expected to exclude larger proportions of affected adults. Recent reviews have suggested that that the use of some exclusion criteria in clinical trials may not be warranted to increase patient safety or increase the internal validity of the study (Spall et al., 2007), or may be poorly operationalized (Humphreys et al., 2005; Humphreys and Weisner, 2000), precluding replication by other investigators. Some of these exclusion criteria are predictors of poor outcome and their use may lead to an overestimate of the efficacy of the intervention being studied. For instance, prior research has shown that the presence of co-occurring disorders including substance use disorders, major depressive disorder, and personality disorders (particularly antisocial personality disorder) in individuals with alcohol dependence is associated with poorer outcomes in alcohol trials and an increased risk of relapse (Dawson et al., 2005; Rounsaville et al., 1987; Tómasson and Vaglum, 1998; Hasin et al., 2002; Bradizza et al., 2006).

It should also be noted that although several criteria are widely implemented, not all trials use all criteria. A recent comprehensive review of clinical trials (Humphreys et al., 2005) found that 17.3% of the studies used one of these criteria, 14.9% used two, 15.9% used three, and approximately 52% used at least four of the aforementioned criteria.

Although most studies reported their eligibility criteria, some did not. Future trials should report how their exclusion criteria were operationalized and how they would likely influence patient eligibility (Moher et al., 2001). While the use of more restrictive eligibility criteria may be appropriate in early efficacy trials, greater attention should be given to justifying trade-offs between the application of each exclusion criterion and its impact on generalizability.

Application of the criteria to the overall sample estimates the potential population generalizability of the clinical trials if all individuals with alcohol dependence were to seek treatment. Application of the criteria to the treatment-seeking subsample, by contrast, estimates the generalizability of clinical trials to those currently in treatment. Despite application of a smaller set of criteria in the treatment-seeking subsample analysis, substantially more subjects were excluded than from the overall sample. Treatment-seeking individuals tend to have greater illness severity and more comorbidity (Cohen and Cohen, 1984). Higher perceived or assessed need, as indicated by the higher rates of psychiatric and medical comorbidity, or legal imperatives may powerfully influence treatment-seeking behaviors among individuals with alcohol dependence (Kirchner et al., 2000; Weisner and Matzger, 2002; Wu and Ringwalt, 2004). Paradoxically, clinical trials may tend to exclude those who have the greatest overall disease burden and therefore the greatest need for treatment.

We selected the NESARC for our study because it is the largest epidemiological study with information on alcohol use disorders in US adults. However, the NESARC may not be the appropriate reference for all disorders or age ranges. In general, selection of the survey used as the reference sample should be guided by the population to which the clinical trial intends to generalize its results. For example, the forthcoming National Comorbidity Survey for Adolescents (NCS-A) may be a better epidemiological sample to assess the generalizability of clinical trial designs for adolescents.

Our current investigation focuses on the *a priori* eligibility of participants. It provides no information on subjects who actually enter those studies. In this way, we estimate an upper bound of the generalizability of clinical trials. In practice, most studies do not achieve representative participation by gender, race/ethnicity and other sociodemographic and clinical variables within the constraints of their eligibility criteria. Differential rates of participation among eligible individuals results in additional loss of generalizability of the

study results. For this reason, the actual ("*a posteriori*") generalizability of the studies is almost always lower than their *a priori* generalizability. Little attention has focused on this important aspect of the generalizability of clinical trials. As the *a posteriori* generalizability of clinical trials decreases, the likelihood that the results will inform clinical practice tends to diminish.

The current study has several limitations. First, we adopted specific conventions to translate clinical criteria to the NESARC sample. Different conventions would have likely yielded different exclusion estimates. However, the percentage of excluded subjects was high both in the full sample and in the subsample of treatment-seekers, and in several previous studies (Humphreys and Weisner, 2000), suggesting that commonly applied criteria are likely to exclude many subjects with alcohol dependence. Second, two of the exclusion criteria summarized by Humphreys et al. (2005) (neurocognitive problems, residential instability) could not be operationalized. Thus, the number of subjects excluded from clinical trials would likely be higher than our estimates. Future epidemiological studies should seek to further increase and improve the operationalization of exclusion criteria in clinical trials, which will help refine estimates of the proportion of individuals ineligible for clinical trials. Third, we applied criteria from a summary of trials that include different types of trials (Humphreys et al., 2005). Effective strategies, such as employment of bilingual staff, the offer of free or inexpensive child care, provision of transportation, may help to increase the representativeness of participants in clinical trials (DelBoca and Darkes, 2007).

Given the pronounced and persistent low treatment rates for individuals with alcohol dependence (Hasin et al., 2007), better knowledge about treatment efficacy across individuals with alcohol disorders with a wide range of characteristics and clinical complexity is important not only for mental health specialists, but also for generalists who provide mental health care. Although these clinicians are likely to encounter individuals with alcohol use disorders in their practices, they may or may not intervene with the alcohol use disorder. Information from more inclusive trials may increase our confidence in treatment efficacy and encourage individuals with alcohol dependence to seek treatment at an earlier stage of their illness.

The prospective generalizability of clinical trials can be estimated by applying their eligibility criteria to epidemiological samples. Traditional alcohol dependence treatment studies are likely to involve highly selected patient samples. Until funding and regulatory agencies emphasize the importance of more inclusive eligibility criteria (Rothwell, 2005), clinical trials are likely to continue to be designed for select populations with the highest probability of a robust treatment response. A greater emphasis on more inclusive study criteria should move the field toward developing interventions that address the broad and varied service needs of the general population with alcohol dependence. Future research should examine the population generalizability of clinical trials for the treatment of other substance use disorders.

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Table 1

Estimated percentage of adults with alcohol dependence in the NESARC excluded from typical clinical trials of treatments for alcohol dependence by traditional efficacy eligibility criteria

Traditional efficacy eligibility criteria (past 12 months)[a]	Current alcohol dependence (*n* = 1484) % (95% CI)	Treatment-seeking sample (*n* = 185) % (95% CI)
Psychotic disorder	1.90 (1.08–3.30)	10.63 (5.21–20.50)
Concurrent alcohol treatment	9.03 (7.44–10.93)	N/A
Medical conditions	24.37 (21.49–27.50)	43.74 (33.45–54.59)
Noncompliance/lack motivation	48.23 (39.40–57.17)	N/A
Demographic (age > 65)	0.96 (0.58–1.59)	0.81 (0.10–6.01)
Illicit drug abuse or dependence	20.69 (17.85–23.86)	38.24 (28.35–49.22)
Social instability (unemployed and unmarried, not students)	5.01 (3.91–6.40)	9.13 (5.18–15.58)
Distance from treatment	7.46 (4.28–12.69)	N/A
Education/literacy	1.19 (0.67–2.11)	1.41 (0.25–7.46)
Legal problems	15.21 (13.00–17.71)	40.50 (31.05–50.71)
Financial situation	30.65 (22.94–39.63)	N/A
Neurocognitive problems[b]	N/A	N/A
Residential instability[b]	N/A	N/A
Overall percentage	50.48 (47.37–53.58)	79.39 (70.30–86.25)

[a] Based on Humphreys et al. (2005).

[b] Information not available on the NESARC.