Representativeness of Patients Enrolled in Influential Clinical Trials: A Comparison of Substance Dependence With Other Medical Disorders

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ABSTRACT. Objective: The purpose of this study was to determine whether randomized trials of treatments for substance dependence differ from those for other medical disorders on quality of enrollment information reporting and sample representativeness. **Method:** Twenty highly cited clinical trials (publication date 2002–2010) of treatments for each of 14 prevalent disorders were identified by structured literature search. The disorders were alcohol dependence, drug dependence, nicotine dependence, Alzheimer's disease, breast cancer, colorectal cancer, chronic obstructive pulmonary disease, depression, diabetes, HIV/AIDS, hypertension, ischemic heart disease, lung cancer, and schizophrenia. The 280 clinical trials were coded for number of individuals screened for eligibility, number of screened individuals meeting eligibility criteria, and number of eligible individuals refusing to participate. **Results:** Substance-dependence treatment trials were significantly more likely to

track and report enrollment information (75% vs. 45% of clinical trials for other disorders, $p < .001$). Substance-dependence trials did not differ from trials focused on other disorders on mean rate of non-enrollment. Across disorders, the primary driver of non-enrollment appeared to be clinical trial exclusion criteria rather than eligible patients refusing to enroll. **Conclusions:** Relative to other disorders, trials in the substance-dependence field do a better (although imperfect) job of tracking and reporting enrollment information. Low enrollment rates and unrepresentative samples are not challenges unique to treatment outcome studies in the substance-dependence field. Across a range of disorders, clinical trials that use eligibility criteria judiciously are more likely to produce findings that generalize to front-line clinical practice than are trials that restrict enrollment to a small and unrepresentative subset of patients. (*J. Stud. Alcohol Drugs*, 74, 889–893, 2013)

RANDOMIZED CLINICAL TRIALS (RCTs) are a uniquely powerful way to evaluate the impact of a treatment in a given sample of participants. However, the conclusions drawn from an RCT are potentially applicable in front-line clinical practice only to the extent that the trial participants resemble real-world patients. If, for example, an RCT of alcohol-dependence treatment excludes all patients who have a comorbid psychiatric disorder, use illegal drugs, or are homeless, an administrator of a Salvation Army residential program in the inner city would be understandably hesitant to apply the trial's findings. A burgeoning body of research has documented that large proportions of individuals with substance use disorders cannot meet eligibility criteria for clinical trials and that trial participants are markedly different from both community samples and treatment seekers.

For example, in the tobacco-dependence field, the median clinical trial has 12 exclusion criteria, and approximately two thirds of smokers in the general population are ineligible under one or more of them (Le Strat et al., 2011). For illicit drug dependence, a review of 98 clinical trials found that less than one third reported information sufficient to calculate the proportion of screened patients who were eligible and the proportion of the eligible group who agreed to participate (Melberg and Humphreys, 2010). In trials reporting such information, 26% of screened patients were ineligible, and a further 32% of the eligible patients refused to participate.

For alcohol dependence, which has been the most extensively studied, 79% of treatment-seeking individuals would be ineligible under at least one prevalent clinical trial criterion (Blanco et al., 2008). Other work has shown that African Americans are particularly likely to be underrepresented in alcohol-dependence trials (Humphreys, 2003; Humphreys and Weisner, 2000; Humphreys et al., 2007) and that, beginning in the 1970s, treatment outcome studies have become increasingly restrictive in their enrollment procedures (Humphreys et al., 2005). The findings of these and other studies, using different methods and samples and conducted by different research teams, converge on the conclusion that participants in substance-dependence treatment outcome studies differ from patients receiving such treatment in the real world.

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Such findings regarding the clinical utility of research are concerning, but it is unclear whether high rates of trial non-enrollment and attendant unrepresentative samples are a particular challenge for substance-dependence RCTs or whether this is a broader issue for clinical trial design and application across medical disorders. Stirman and colleagues' (2005) cross-disease comparison concluded that research on substance-dependence psychotherapies was unique among psychiatric disorders in being unusually unrepresentative of the patient population. This observation will resonate with some practitioners' clinical experience: Particularly in the public sector, many substance-dependence patients have multiple comorbidities and life problems (Stöffelmayr et al., 1989), which would tend to exclude them from trials or make them unlikely to consent to participate if they were eligible (e.g., sociopathy, extreme anxiety or paranoia).

Yet research in other areas suggests that the challenge of unrepresentative samples may be more general. Hlatky and colleagues (1984), for example, found that between 87% and 96% of cardiovascular disease patients in an observational database would not have been eligible for the field's most influential trials. Haberfellner (2000) reported an even starker result in a study of depressed patients seen in community practice. Of 216 consecutively screened patients, 215 did not meet eligibility criteria for a clinical trial of antidepressant medication. (The 216th refused to participate.) Other reports of low enrollment and unrepresentative samples have come from fields as diverse as nephrology and oncology (Blosser et al., 2011; Clément-Duchêne et al., 2008).

Poor reporting complicates accurate assessment of the representativeness (or lack thereof) of clinical trial samples. Gross and colleagues (2002) documented that the reports of only 28% of a sample of 172 clinical trials across a range of disorders provided sufficient information to assess the proportion of patients who were enrolled and that, in at least some cases, this was the result of study teams not tracking this information during recruitment, perhaps because they did not consider it important. On the general principle that one is more likely to find something if one carefully looks for it, one explanation for why particular fields of treatment research have apparently high levels of non-enrollment may be that, in such fields (the substance use disorders treatment field being an excellent example), the issue has received extensive attention and therefore research teams have put more effort into tracking and reporting non-enrollment.

To investigate these issues, our research team assembled a database of 280 highly cited RCTs of treatments for a range of disorders, including but not limited to dependence on alcohol, illicit drugs, and nicotine. Our initial study of this database found that the mean non-enrollment rate in RCTs was 40.1% and that the quality of reporting of enrollment information had improved markedly from 2002 to 2010

(Humphreys et al., 2013). The present study uses this same database to examine whether the quality of reporting and the level of non-enrollment vary between studies focused on substance dependence and those focused on other medical disorders.

Method

Using methods and search terms described in Humphreys et al. (2013), we assembled a database of 280 RCTs, with 20 trials for each of the following 14 disorders: alcohol dependence, drug dependence, nicotine dependence, Alzheimer's disease, colorectal cancer, chronic obstructive pulmonary disease (COPD), depression, diabetes, HIV/AIDS, hypertension, ischemic heart disease, lung cancer, and schizophrenia. A publication date range of 2002–2010 was chosen to capitalize on the impact of the 2001 Consolidated Standards of Reporting Trials (CONSORT) Statement, which recommended that publications of RCTs include detailed enrollment information (Moher et al., 2001).

To standardize comparisons across disorders and to ensure that our analysis focused on RCTs that had some impact in their field, the sample was limited to the 20 most highly cited studies for each disorder. *Highly cited* was defined as citations per year to allow later studies to have a reasonable chance to rank as influential (Humphreys et al., 2013).

Research assistants double-coded the studies on the number of people with the disorder of interest who were screened for trial eligibility, the number of those who met trial eligibility criteria, and the number of eligible individuals who agreed to participate. If a study noted that some people who were initially screened did not have the disorder of interest, as is common in studies that recruit from the general population rather than in clinical settings, these individuals were removed from all calculations because they do not represent the population to which the study is attempting to generalize. Reason for non-enrollment was recorded when it was available in the published report. Non-enrollments were coded as due to trial exclusion criteria, refusal to participate, or other reasons (e.g., administrative errors).

Results

The 60 studies of substance-dependence (alcohol, other drug, tobacco) treatments were significantly more likely than the 220 studies of treatments for other disorders to report information regarding enrollment. A total of 75% of the substance-dependence treatment studies included such information compared with only 45% of studies of treatments for other disorders, $\chi^2(1) = 16.5, p < .001$. Were the 20 disorders ranked by quality of trial enrollment information, the three substance-dependence categories

would appear in the top five. The RCTs of depression and of alcohol dependence both reported enrollment information in 80% of cases (16 of 20), nicotine-dependence treatment trials did so in 75% of cases (15 of 20), and Alzheimer's disease and drug-dependence trials both did so in 70% of cases (14 of 20). Despite the CONSORT statement, reporting of enrollment information was rare for some disorders, including breast cancer (2 of 20 trials) and colorectal cancer (3 of 20 trials).

Within the 145 studies providing sufficient enrollment information, studies focused on substance dependence ($n = 45$) were compared on non-enrollment rate with those addressing other disorders ($n = 100$). Although substance-dependence trials had a mean non-enrollment rate of 45.5% ($SD = 21.7$) versus 37.7% for other disorders ($SD = 24.2$), this difference was not statistically significant. In rank order, the rate of non-enrollment was highest for ischemic heart disease ($M = 63.9\%$, $SD = 28.6$, $n = 6$), followed by breast

cancer ($M = 60.3\%$, $SD = 51.1$, $n = 2$), drug dependence ($M = 51.7\%$, $SD = 22.8$, $n = 14$), depression ($M = 50.2\%$, $SD = 27.0$, $n = 16$), alcohol dependence ($M = 45.2\%$, $SD = 20.1$, $n = 16$), nicotine dependence ($M = 40.1\%$, $SD = 22.4$, $n = 15$), diabetes ($M = 39.2\%$, $SD = 18.7$, $n = 11$), schizophrenia ($M = 37.5\%$, $SD = 29.5$, $n = 9$), HIV/AIDS ($M = 36.3\%$, $SD = 19.2$, $n = 13$), colorectal cancer ($M = 33.7\%$, $SD = 13.7$, $n = 3$), COPD ($M = 32\%$, $SD = 19.4$, $n = 9$), lung cancer ($M = 31.1\%$, $SD = 26.8$, $n = 8$), Alzheimer's disease ($M = 25.6\%$, $SD = 9.5$, $n = 14$), and hypertension ($M = 25.1\%$, $SD = 22.4$, $n = 9$).

Slightly more than one third (35%, $n = 98$) of studies provided sufficient information to break down reasons for non-enrollment into categories (Figure 1). The number of disease categories with low n s (half had six or fewer studies) precludes reliable inferential statistical tests on these data. Descriptively, however, the proportion of patients that is ruled out of enrollment by exclusion criteria (some of

FIGURE 1. Mean percentage of participants not enrolled in clinical trials, by reason. Note: None of the breast cancer treatment randomized clinical trials reported the above information. COPD = chronic obstructive pulmonary disease.

whom, of course, may have refused to enroll if eligible) is larger than the proportion that was eligible but refused to participate both in trials of substance-dependence treatment and in those focused on other disorders.

Discussion

The primary difference regarding non-enrollment in studies of treatment for substance dependence versus treatment for other disorders is not the level of non-enrollment but researchers' habits of tracking and reporting such information. Simply said, most highly cited, recent RCTs in the substance-dependence field have tracked and reported the enrollment information required by CONSORT, whereas most highly cited trials in other fields (e.g., oncology, cardiology) have not. This is not to say that the substance-dependence treatment field should be complacent regarding reporting: 25% of even its most highly cited trials did not adequately report enrollment information, and broader reviews of the literature encompassing all trials (highly cited or not) find even higher rates of inadequate reporting (Melberg and Humphreys, 2010).

The higher rate of tracking and reporting enrollment information in substance-dependence RCTs might have biased the present study to find a significantly higher level of non-enrollment in substance-dependence trials versus levels for other disorders (i.e., as an artifact of better reporting), but no such difference emerged. High levels of non-enrollment and resultant unrepresentative samples are not a research challenge unique to substance-dependence trials.

Non-enrollment rates averaged between 25.1% and 63.9% across disorders, suggesting that for no disorder is it a negligible concern. Even if only a quarter of individuals with an illness are not enrolled, this can raise study cost by extending recruitment time. It will also lower external validity because a more highly selected sample (e.g., those who meet particular eligibility criteria) by definition differs from the population of patients from which it is drawn. Concerns about unrepresentativeness rise in tandem with the proportion of patients not enrolled (Humphreys et al., 2007).

Some researchers may be hesitant to use fewer exclusion criteria and thereby enroll a higher proportion of patients because they believe that doing so inevitably increases within-condition heterogeneity in treatment response, which reduces statistical power. Whether any given exclusion criterion produces this effect should be viewed as a hypothesis rather than a certainty, however. Perhaps because response to alcohol treatment is hard to predict, research in the alcohol-treatment field has found that commonly used exclusion criteria tend to increase—rather than decrease—heterogeneity in treatment response (i.e., reduce statistical power to detect an effect; Humphreys et al., 2008).

Clearly, not all patients should be enrolled in trials, particularly when an experimental treatment may pose a risk to safety. Like many other commentators, however, we advocate that treatment researchers use exclusion criteria judiciously and only with solid justification (Van Spall et al., 2007). Also, RCTs can increase sample representativeness by using comparison conditions that appear fairly similar to potential participants, as this can decrease rates of refusal to be randomized (Melberg and Humphreys, 2010). Finally, for the sake of patients and clinicians, researchers should take care to fully report whatever decisions they make about enrollment criteria and the impact of those decisions on their findings. The results presented here suggest that although non-enrollment and sample unrepresentativeness in treatment outcome research has been studied unusually extensively in the substance-dependence field, these suggestions for trial design merit discussion across a broad range of disorders.

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