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Review

The exclusion of people with psychiatric disorders from medical research

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ABSTRACT

People with psychiatric disorders are excluded from medical research to an unknown degree with unknown effects. We examined the prevalence of reported psychiatric exclusion criteria using a sample of 400 highly-cited randomized trials (2002–2010) across 20 common chronic disorders (6 psychiatric and 14 other medical disorders). Two coders rated the presence of psychiatric exclusion criteria for each trial. Half of all trials (and 84% of psychiatric disorder treatment trials) reported possible or definite psychiatric exclusion criteria, with significant variation across disorders ($p < .001$). Non-psychiatric conditions with high rates of reported psychiatric exclusion criteria included low back pain (75%), osteoarthritis (57%), COPD (55%), and diabetes (55%). The most commonly reported type of psychiatric exclusion criteria were those related to substance use disorders (reported in 48% of trials reporting at least one psychiatric exclusion criteria). General psychiatric exclusions (e.g., "any serious psychiatric disorder") were also prevalent (38% of trials). Psychiatric disorder trials were more likely than other medical disorder trials to report each specific type of psychiatric exclusion (p's < .001). Because published clinical trial reports do not always fully describe exclusion criteria, this study's estimates of the prevalence of psychiatric exclusion criteria are conservative. Clinical trials greatly influence state-of-the-art medical care, yet individuals with psychiatric disorders are often actively excluded from these trials. This pattern of exclusion represents an under-recognized and worrisome cause of health inequity. Further attention should be paid to how individuals with psychiatric disorders can be safely included in medical research to address this important clinical and social justice issue.

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1. Introduction

People with psychiatric disorders experience cancer, heart disease and other medical disorders at rates as high or higher than the rest of the population. However, they are underrepresented in trials of treatments for these disorders because investigators – with the best of intentions – design research protocols that do not permit people with psychiatric disorders to enroll (Humphreys et al., 2005; Stapleton, 2010). This pattern of exclusion is seen within psychiatric medical research (e.g., excluding patients with alcohol use disorders from enrolling in clinical trials of depression treatment) and outside of it (e.g., excluding patients with psychotic disorders from clinical trials of cancer treatment).

The most common ethical arguments for excluding people with psychiatric disorders from medical research – which may lack empirical support (Roberts et al., 2006) – are that they may be more vulnerable to exploitation due to decisional capacity deficits or greater susceptibility to coercive pressures, and, may be objectively at higher risk of harm in cases where the researched treatment (e.g., aggressive chemotherapy) could impose stress that might exacerbate their psychiatric disorder. Exclusion criteria can also be argued for on statistical grounds: If those with psychiatric disorders have markedly different outcomes than those without such disorders, the power of a trial to detect the effect of a medical treatment is lessened (Lipsey, 1990).

Yet from a different perspective, the exclusion of people with psychiatric disorders from medical treatment research may be considered unethical. Because psychiatric conditions are highly prevalent and often co-occur with other medical illnesses, declining to study people with psychiatric disorders could be considered a serious form of scientific neglect and therefore a social injustice. Results derived from clinical research guide state-of-the-art medical practice in the health care system, particularly if a trial is widely-cited and high profile (Rothwell, 2005). If people with psychiatric disorders respond differently to a treatment (e.g., a newly developed pain medication interferes with metabolization of their psychiatric medication) but are not included in the research evaluating it, the disparate impact will not be known until they receive that treatment on a broad scale in the health care system. In that sense, excluding people with psychiatric disorders from medical research may not so much reduce their risk of harm as shift it from a small number of people in a research study to a far larger number of people in the health care system. Because tens of millions of Americans have psychiatric disorders – including some highly vulnerable subpopulations (Martins et al., 2012) – the cumulative impact of this shifting of risk into everyday health care provision could exacerbate existing health disparities and erode public confidence in the value of the medical research enterprise.

As for whether exclusion is justified because it increases statistical power, this depends on whether the moderators of treatment outcome are known. With new treatments, whose main effect is not even established, knowing moderators in advance is logically impossible. Even for widely employed treatments, evidence suggests that researchers can guess wrong and find that an exclusion criterion has lowered rather than raised a clinical trial's statistical power (Humphreys et al., 2008). From an ethical perspective, one should further consider the question of why it is acceptable is to exclude people with psychiatric disorders from participation as the primary solution, rather than refining scientific designs or augmenting statistical power in other ways, such as improving reliability of measurement or increasing sample size (Kraemer and Thiemann, 1987).

Irrespective of where researchers come down in this debate, it would be highly useful to all parties to know the basic facts: How often are people with psychiatric disorders actually excluded from medical research, and which sorts of individuals are excluded? Accordingly, the present study engages these questions by examining the enrollment practices of the most widely-cited clinical trials of recent years, both within and without psychiatric medicine.

2. Materials and methods

Using standardized search terms across databases in Web of Science (see Humphreys et al., 2013), we identified the 20 top-cited randomized controlled trials with results published from 2002 to 2010 for each of a varied group of 20 prevalent chronic disorders (i.e., a total sample of 400 trials). A starting date of 2002 was chosen because the CONSORT criteria were revised in 2001 to clarify that reporting of enrollment procedures was required for clinical trials (Moher et al., 2001). To avoid a bias toward older studies, "Top-cited" was defined as average number of citations per year since publication rather than total number of citations. The specific search terms used for each disorder and the number of hits are included in a supplemental appendix.

Medical disorders within and without psychiatry were included: alcohol use disorder, Alzheimer's disease, asthma, breast cancer, chronic kidney disease, chronic obstructive pulmonary disorder (COPD), colorectal cancer, depression, diabetes mellitus, drug use disorder, gum disease, human immunodeficiency virus (HIV)/AIDS, hypertension, ischemic heart disease, low back pain, lung cancer, osteoarthritis, prostate cancer, schizophrenia, and tobacco use disorder. These disorders were selected because they collectively account for the bulk of mortality and functional burden in the U.S. population (Holt et al., 2015).

Each widely-cited clinical trial was double-coded by two trained coders. If necessary information was lacking in the included publication, the coders also examined other publications related to the same trial for further details. The coders evaluated all psychiatric exclusion criteria other than those related to the disorder of interest (i.e., they did not code the criterion when a trial of a schizophrenia treatment mentioned that subjects without schizophrenia were excluded). The coders evaluated whether the trial reported any definite psychiatrically-related exclusion criteria (e.g., "patients with suicidal ideation were excluded") and whether it reported any criteria that would possibly exclude individuals with psychiatric disorders. This latter category was coded positively when the publication listed a broad, often subjective, reason for exclusion, such as excluding for "serious conditions" or "uncontrolled medical conditions." Trials could be coded positively for both definite and possible psychiatric exclusion criteria (e.g., a trial that excluded for use of a psychiatric medication [Definite] as well as "any condition that may have complicated the informed consent process" [Possible]).

When psychiatric exclusion criteria were reported, the coders recorded whether they were general (e.g., "any unstable/serious psychiatric condition") and/or mentioned a specific psychiatric diagnosis or symptom. The presence or absence of a number of specific psychiatric exclusion criteria were also coded (i.e., substance use disorders, suicidality, use of psychiatric medications, psychotic disorders).

The coders trained on 10% ($n = 40$) of the trials, and continued to monitor reliability throughout the coding process to resist coder drift. The coders maintained a high level of reliability (pooled kappa of 0.81 and 94% agreement across the coded variables). When raters disagreed, the responses were averaged (i.e., if one coder responded "1 = yes" for presence of psychotic criteria and the other responded "0 = no," our analysis database included "0.5" for that item). This approach generates better reliability and validity than does attempting to reach consensus through discussion about each