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Participant exclusion criteria in treatment research on neurological disorders: Are unrepresentative study samples problematic?

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ABSTRACT

Objective: Exclusion criteria are an important determinant of the external validity of treatment research findings, yet the prevalence and impact of exclusion criteria have not been studied systematically. Our objective was to describe prevalent exclusion criteria in treatment research on neurological disorders and to analyze their impact on sample representativeness and generalizability of findings.
Design: Narrative literature review of studies focusing on treatment for neurological disorders. Studies were identified from PubMed and bibliographies.
Results: Eight studies were included in the narrative review: 3 studies focused on Alzheimer's disease/dementia, 2 each focused on traumatic brain injury (TBI) and epilepsy, and 1 focused on amyotrophic lateral sclerosis (ALS). The total number of patients screened across all studies was 20,018, of which 14,721 (73.5%) were excluded. An average of 6 exclusion criteria was applied. The criteria that contributed most to exclusion were the presence of comorbid psychiatric conditions, a history of alcohol or other substance misuse, and cognitive impairments. Women and the elderly were underrepresented among included samples. Race/ethnicity proportions were seldom reported.
Conclusion: Exclusion criteria are used extensively in neurological treatment research and prevent about 3 in 4 patients from participating in research. This limits the generalizability of current findings. Further, because excluded individuals are disproportionately from vulnerable populations, extensive exclusion also raises ethical concerns. Exclusion criteria should be used only in cases where there is a strong rationale so that neurological treatment research can make a greater impact on clinical care.

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1. Introduction

Millions of Americans live with adult-onset neurological disorders; worldwide hundreds of millions do so [1,2]. People with neurological disorders span the developmental spectrum: disorders such as dementia and Parkinson's disease are aging related, whereas others, such as epilepsy or traumatic brain injury (TBI), may strike at any age [3]. Significant research efforts have been made to evaluate treatment options for these diverse disorders, including pharmacotherapy, behavioral management, occupational therapy, and deep brain stimulation. Whether such treatment research can inform clinical practice depends on the similarity between research and clinical samples, which in turn are shaped by enrollment exclusion criteria in treatment research.

Some exclusion criteria are implemented to ensure the safety and protection of human subjects. For example, some patients may have medical conditions which make an evaluated treatment risky. Others may lack decisional capacity to provide informed consent. That said, extensive exclusion criteria can result in research samples that do not represent the diversity, symptom complexity, or daily challenges of the clinical population [4,5]. This downside underscores the need to select exclusion criteria thoughtfully to include the most representative sample possible while maintaining scientific and ethical integrity [6,7]. However, many studies do not provide clear rationales for the exclusion criteria they adopt. Taylor et al. reviewed 434 studies published in Journal of the American Geriatrics Society and found that 94% of the studies did not provide justification for using cognitive impairment as an exclusion criterion in geriatric research. Furthermore, only 43% provided a breakdown of key reasons for exclusions in the eventual sample, and only 14% discussed exclusion as a possible limitation. In another report, Van Spall et al. [8] conducted a review of eligibility criteria used in trials that were published in high impact general medical journals. They found that 84.1% of trials included at least one poorly justified exclusion criteria on that only 47.2% of reviewed studies had well-justified exclusion criteria.

Investigators and policy makers are beginning to recognize the problems inherent in the overuse of exclusion criteria in neurological treatment studies. For example, the IMPACT [9] statement for TBI recommends minimizing the use of exclusion criteria and using statistical

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methodology to handle the potential for heterogeneity in treatment response to reduce statistical power. Determining whether such a recommendation would be warranted for other neurological conditions requires synthesis of existing practices across treatment studies and a summary of how those traditions have influenced sample representativeness and study outcomes. Therefore, the objective of the current review was three-fold: 1) to characterize common exclusion criteria in neurological disorder treatment research, 2) to quantify how widely-used exclusion criteria affects the generalizability of research findings to clinical populations and 3) to make recommendations to enhance the external validity, ethical value and accurate reporting of future studies.

2. Methods

Our project team has developed a series of structured literature reviews called the Cross-Disease Review of Exclusion Across Medicine (CREAM). Detailed methodology of the CREAM literature review process, which integrates findings on exclusion criteria and their impact across various medical conditions, is provided in Humphreys (2014) [10], and is similar to PRISMA recommendations [11]. Literature was identified primarily by conducting English-language searches in PubMed (from inception to July 2013) and cross-referencing against Google Scholar (inception to February 5, 2015[2]) using the following terms: 'Eligibility criteria and generalizability' (anywhere in paper), 'exclusion criteria and generalizability' (anywhere in paper), 'exclusion criteria' (in title of paper) and 'eligibility criteria' (in title of paper). This search strategy generated 326 articles across all diseases. Additional references were identified from the bibliographies of selected studies and were also discovered incidentally.

This review focused on neurological disorders that had primary onset in the brain, such as dementia and traumatic brain injury. Conditions that represented neurological sequelae of other disorders, such as cerebrovascular disorders, were excluded. Within relevant clinical conditions, studies were included if they analyzed the prevalence and nature of exclusion criteria in treatment research studies of relevant neurological disorders, and/or analyzed the impact of exclusion criteria on sample representatives or study results. To be included, studies had to analyze how the exclusion criteria affected sample representativeness or study outcomes. For example, a clinical trial that simply mentioned its exclusion criteria or rate was not included in this review, but a substudy from the same trial that analyzed how those criteria influenced the study sample's similarity to a real-world sample of unselected patients would be included. Refusal to participate was not considered synonymous with exclusion criteria because the predictors and nature of being excluded from research differ from those of being judged eligible but declining to participate [12]. Where data were provided, percent ineligible was calculated based as the number ineligible/number screened.

3. Results

We identified 8 studies that assessed the representativeness of clinical samples in neurological treatment research. Of those, 2 empirical studies [13,14] and 1 review [15] focused on Alzheimer's disease/dementia, 2 each focused on TBI [16,17] and epilepsy [18,19], and 1 focused on amyotrophic lateral sclerosis (ALS) [20]. Included studies either (1) applied exclusion criteria from treatment research studies to a clinical population to determine how many patients within the clinical sample would be excluded were the research criteria applied, or, (2) examined all patients screened for study participation and compared those who were included and those who were excluded.

Across all study samples, the total number of unique patients screened for participation was 20,018 of which 14,721 were excluded from participation. Primary research studies are summarized in Table 1 and reviews are summarized in Table 2. Key findings from each of these studies are summarized next, grouped by specific disease conditions.

3.1. Alzheimer's disease (AD)

Almici et al. [13] presented a brief overview of 9 pharmacological RCTs conducted on outpatients with AD. Of 745 AD patients, 218 (29.3%) were excluded due to physical comorbidities and/or use of drug therapy. Of the 527 remaining individuals, a further 360 (68.3%) were excluded because their caregiver was unavailable or due to logistic problems. These trials ultimately enrolled 109 patients, indicating an exclusion rate of 85.4%. Although the lack of detail in this report left many questions unanswered, it was clear that exclusion rates were high, raising the issue whether it would be appropriate to generalize these results from research to clinical practice.

To determine whether clinic populations are well represented in AD trials, Schneider et al. [14] applied exclusion criteria of two Phase III large trials to a clinical registry of 3470 patients with a diagnosis of "probable AD" or "possible AD." The two trials excluded patients with "significant" medical and psychiatric comorbidities, history of substance use disorders, and those patients living alone. Both trials also excluded patients with cognitive impairment based on Mini-Mental Status Exam (MMSE) [21] scores, although they used slightly different cutoffs. The authors found that applying the trial criteria would exclude 94.8% of clinical registry patients from trial participation. Having significant psychiatric comorbidities alone disqualified 62.7% of patients with possible AD and 59.6% of those with probable AD. More Blacks than Whites would be excluded across both "probable AD" and "possible AD" samples. Specifically, 7.6% of all excluded patients were Black, whereas 3.3% of all included patients were Black. The reverse was true for Whites, in that Whites composed of 77.7% of all excluded patients but 94.6% of all included patients. Women composed only 52.3% of included participants compared to 71% of the excluded patients, indicating that the exclusion criteria led to female patients being underrepresented. Those excluded were also slightly older (average of 76.3 years of age vs 72.9 for included patients). Finally, those who were excluded had cognitive functioning compared to those deemed eligible for trial. Although there was considerable variability in the 9 sites, even at the highest recruitment site, 85% of patients would be disqualified from participating in the trials. The differences between the excluded and included groups were especially worrisome given that the trials were Phase III and as such were designed to evaluate generalizability of AD treatments.

These and a few other studies were included in a recent systematic review and meta-analysis by Cooper et al. (2014) [15]. The review estimated the number of dementia patients in a clinical sample who might be considered for treatment trials using common exclusion criteria. This review noted that among higher quality studies, 74% of patients with probable AD would be excluded. Across the 12 studies reviewed, older age, female gender, and lower education levels were predictive of higher exclusion rates.

3.2. Traumatic brain injury (TBI)

Slieker et al. [16] assessed patient selection in TBI treatment research by reviewing screening logs from two Phase III RCTs: the Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk (SAPHIR) and the Dexanabinol trial. Both trials were efficacy studies of neuroprotective agents. SAPHIR was conducted in 54 European centers and the dexanabinol trial took place in Europe, Israel, Australia, and the United States. A review of screening logs found that 2594 patients in SAPHIR (74% of all screened patients) and 5972 patients in dexanabinol trials (85% of all screened patients) did not meet enrollment criteria and were excluded. The most common exclusion reasons were clinical neurological status (a criteria met by 29% of patients for SAPHIR and

[2] Initial search was conducted in June 2013, which was updated in February 2015.