Exclusion criteria and generalizability in bipolar disorder treatment trials

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ABSTRACT

Objective: The current paper reviews the English-language research on exclusion criteria in bipolar disorder treatment trials and discusses how study samples compare to the general bipolar patient population.
Methods: & Results: Across 8 identified studies of exclusion criteria and their impact, between 55% and 96% of people with bipolar disorder would be excluded from treatment research. The number of exclusion criteria varies across bipolar disorder treatment research, with one study estimate of a median of 7 criteria used across studies. The criteria that excluded the greatest number of potential participants were comorbid substance use disorder, suicidal risk, and comorbid medical conditions. Both studies that compared treatment responses among participants who met and did not meet exclusion criteria found no statistically significant differences.
Conclusions: Most potential participants are excluded from outcome research, which creates challenges for recruitment and limits generalizability of study findings. Common exclusionary practices lead to unrepresentative samples that limit generalizability and reduce the confidence of clinicians that findings can be translated to front-line practice with bipolar disorder patients.

1. Introduction

Bipolar disorder affects 4.4% of the population at some point in their lifespan [1] and often causes significant disruptions to work, social, and family life domains [2] as well as increased suicidal risk [3]. The nature of bipolar disorder and its comorbidities present unique challenges to treatment researchers, including how to select exclusion criteria that balance rigor and relevance [4]. More stringent exclusion criteria can increase the likelihood that a sample will respond to an evaluated treatment in a homogeneous fashion, which enhances statistical power. Yet, exclusion criteria by definition widen the gap between research samples and clinical populations, thereby threatening external validity.

Clinical trials across a range of psychiatric disorders have traditionally attempted to recruit samples of individuals with symptoms (and related impairment) that emanate exclusively from their primary diagnosis [5]. This approach to sample selection has raised concerns regarding the generalizability of research samples to 'real-world' community patient populations, most particularly whether "evidence-based" treatments are effective for the severely troubled patients who tend to be excluded from clinical trials [6]. Some exclusion criteria are essential to treatment research in order to protect human subjects from

potential harm (e.g., adverse medication interactions). Yet others are optional and, as such, it is important to consider how the exclusion criteria may influence study samples and the implications of potentially biased samples regarding the generalizability of treatment effects. This paper reviews the literature on the exclusion criteria that have been employed in bipolar disorder treatment research, the proportion of patients excluded, and how exclusion criteria may affect the generalizability of results.

2. Methods

The Cross-disease Review of Exclusion Across Medicine (CREAM) project is assessing the impact of exclusion criteria in research conducted across a range of medical specialties (e.g., psychiatry, oncology, rheumatology). A detailed description of the literature review procedure can be found in Humphreys [7]. Literature was primarily identified by conducting English-language searches in PubMed (Original Date of Search: July 8, 2013) on 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 generated 326 unique articles, all of which were reviewed by one of the authors, as were relevant

references within those articles. An updated search was conducted on August 19, 2016, which yielded an additional 160 unique articles. Other articles were discovered in a frankly opportunistic fashion. From this cross-disease pool of literature, evidence related to specific diseases were synthesized within focused reviews for a range of diseases, including depression [8], neurological diseases [9], schizophrenia [7], anxiety disorders [10], and substance use disorders [11]. The present review focuses on those identified treatment studies that address overall and/or specific criteria exclusion rates for bipolar disorder.

To be considered relevant to the CREAM project, studies had to analyze data on (1) the prevalence and nature of exclusion criteria, and/or (2) the impact of exclusion criteria on sample representativeness or study results. Clinical trials that simply reported their exclusion rate were not included in this review. Non-participation in research based on lack of informed consent by eligible participants has quite different implications than exclusion based on factors selected by the researchers. For this reason, lack of informed consent was not considered as an exclusion criterion in the current review.

3. Results

All included studies (N = 8) evaluated baseline differences between included and excluded participants in bipolar disorder treatment studies and two studies also examined outcome differences. Major findings are summarized in Table 1. Potential subjects excluded based on specific exclusion criteria within each study is presented in Table 2.

Licht and colleagues [12] examined a sample of 164 prospective participants who were deemed eligible for a research study based on initial screenings, comparing those who were subsequently included versus excluded based on various criteria. This sample was drawn from inpatients with manic symptoms who had been consecutively admitted to a university hospital. Thirty-nine percent of the sample was excluded for "methodological reasons" (defined as receiving treatment up to the time of admission), and another 32% were excluded based on "non-compliance." Another 4% were excluded for "safety reasons," which encompassed having a major medical illness, being pregnant, known contraindications to the pharmacological treatment of interest, and/or being in an "extreme manic state requiring other treatment." The

combined effect of the criteria was to exclude 84% of the participants who had already been deemed eligible during initial screenings.

Talamo, Baldessarini, and Centorrino [13] reviewed 21 randomized clinical trials (RCTs) conducted between 1998 and 2008 and identified 16 exclusion criteria that were widely-used, non-overlapping and which they had the data to operationalize in medical records of a sample of 67 bipolar inpatients who had received antipsychotic, antimanic, or mood-stabilizing medicines and had a diagnosis of mania or a mixed manic-depressive state at the time of discharge. Medical record data were most commonly excluded based on patients' comorbid substance use (52%) and a recent suicide attempt (38%). A total of 78% of potential participants' records were excluded by at least one criterion, which is a conservative estimate of what would be obtained in real-world patient samples because Talamo et al.'s sample had already been subjected to some exclusion criteria before being selected for analysis. No statistically significant differences were found between excluded and included patient records based on several demographic variables (including age, gender, marital status, employment, education), illness history, current clinical presentations, or treatment outcome. Regarding treatment received, however, the excluded patients were 24% more likely to receive 2 or more psychotropic agents at discharge, which may have influenced their treatment outcome. Data only captured a constrained period of time (11–13 days), which may have also limited ability to detect differences.

Zarin, Young, and West [14] identified a set of 3 exclusion criteria based on 2 published RCTs for valproate and applied them to a sample of DSM-IV diagnosed bipolar disorder patients (N = 92) drawn from routine psychiatric practice. All patients in these samples were receiving psychiatric services at the time of data collection. A total of 39% of the sample would have been excluded for a substance use disorder diagnosis, 22% for uncontrolled major medical conditions, and 6% for central nervous system/neuromuscular disorders. Despite only 3 criteria being evaluated, 55% of the sample was excluded under at least one criterion.

Sachs et al. [15] used a sample of 504 potential participants with a primary diagnosis of bipolar disorder, manic or mixed episode from across 47 centers to compare signal detection based on diagnostic criteria as applied by either clinical raters or a computerized assessment.

Table 1
Summary of study finding.

First author (Year)	Sample size and characteristics	Criteria that excluded the most potential participants (exclusion rate by criterion)	Exclusion rate
Licht (1997)	164 inpatients with manic symptoms	1) "Methodological reasons" (39%) 2) "Non-compliance" (32%) 3) "Safety reasons" (4%)	84%
Talamo (2008)	67 bipolar, acutely manic inpatients	1) Comorbid substance use (52%) 2) Recent suicide attempts (38%) 3) Violent acts (23%)	78%
Zarin (2005)	92 patients with acute mania currently receiving psychiatric services	1) Comorbid substance use (39%) 2) Uncontrolled major medical disorders (22%) 3) Central nervous system/neuromuscular disorder (6%)	55%
Sachs (2012)	504 bipolar patients with manic or mixed episode from across 47 centers	Individual criteria not examined.	64%
Hoertel (2013)	785 bipolar depression and 724 bipolar mania community dwelling patients	1) Comorbid substance use (36%, 36%) 2) Suicide risk (24%, 21%) 3) Comorbid medical condition (20%, 19%)	58%, 56%
Bowden (1995)	179 participants and 577 potential participants with acute mania	1) Failure to meet diagnostic criteria (32%)	Not available
Zimmerman (2016)	Not available (Analysis conducted at study-level; 22 studies)	1) Depressive symptom severity 2) Suicidal ideation 3) Alcohol/drug use disorder 4) Comorbid psychiatric disorder 5) Duration of current depression episode 6) Current manic symptoms	Not available
Filkowski (2015)	163 treatment-refractory bipolar patients referred from physicians, self, or family	1) Psychiatric comorbidity (48%) 2) No prior ECT (32%) 3) Not meeting minimum severity requirements (21%)	96%

Note. The Filkowski et al. (2015) study was unique in studying deep brain stimulation. The results from this study may not generalize to studies of other treatment types.