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Have Treatment Studies of Depression Become Even Less Generalizable? A Review of the Inclusion and Exclusion Criteria Used in Placebo-Controlled Antidepressant Efficacy Trials Published During the Past 20 Years

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Abstract

Objective: To compare the inclusion and exclusion criteria used in antidepressant efficacy trials (AETs) published during the past 5 years with those used in studies published during the previous 15 years.

Patients and Methods: We conducted a comprehensive literature review of placebo-controlled AETs published from January 1995 through December 2014. We included trials whether or not the medication has received regulatory approval for the treatment of depression. We compared the inclusion and exclusion criteria of studies published during the past 5 years (2010-2014) with those of studies published during the previous 15 years (1995-2009).

Results: We identified 170 placebo-controlled AETs published during the past 20 years, 56 of which were published during the past 5 years. The more recent studies were significantly more likely to exclude patients with comorbid Axis I disorders and personality disorders, patients with the episode duration either too long or too short, and patients who had made a suicide attempt in the past. The severity threshold on depression rating scales required for inclusion was higher in the more recent studies.

Conclusion: The inclusion and exclusion criteria of AETs have become more stringent over the past 5 years, thereby suggesting that AETs may be even less generalizable than they were previously (when concerns about their generalizability had already been raised).

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Questions about the generalizability of antidepressant efficacy trials (AETs) to patients treated "in the real world" have been raised for decades. Early studies addressed this issue by comparing the demographic, clinical, and treatment response characteristics of AET participants recruited by advertisements ("symptomatic volunteers") with those of participants referred from clinical settings. These studies found that the 2 groups were generally similar, thereby supporting the generalizability of AETs.[1-5] Other studies examined how many patients applying for an acute phase efficacy trial were accepted into the trial and found low participation rates.[6,7]

The representativeness of samples treated in AETs was most directly examined by applying the inclusion and exclusion criteria to clinical samples. More than a decade ago, our clinical research group found that most depressed patients presenting for treatment to our outpatient practice would have likely been excluded from an AET because they did not meet the study's inclusion and exclusion criteria.[8] Subsequent studies replicated our finding that most depressed outpatients treated in clinical practice would not qualify for an AET.[9-11] Moreover, there was some evidence that treatment response differed between outpatients who would and would not qualify for an AET.[10]

We previously conducted a limited review of the psychiatric inclusion and exclusion criteria used in AETs by examining the criteria

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of 39 AETs published between 1994 and 2000 in 5 journals.[12] In the present report, we conducted a comprehensive review of placebo-controlled AETs published during the past 20 years to determine whether there have been any changes in these criteria subsequent to the publications that highlighted the unrepresentativeness of the samples studied in AETs. We hypothesized that the increased attention given to the lack of generalizability of AETs would result in a broadening of the inclusion and exclusion criteria for study participation.

PATIENTS AND METHODS

Literature Review

To ascertain the sample of studies of AETs, we first reviewed the tables of contents of 49 journals from January 1995 through December 2014. The journals reviewed were those that had published studies included in previous comprehensive reviews of placebo-controlled AETs.[13,14] This was supplemented with a search of the MEDLINE (via PubMed), Embase (via Ovid), and PsychINFO (via EBSCO*host*) databases for the same time period. We used the search terms *depression* or *depressive* and *placebo*. Only articles published in English were included. We also examined the reference lists of meta-analyses of AETs and the studies identified from our literature review.

We did not include trials focused on refractory depression, chronic depression, and bipolar, psychotic, atypical, or melancholic subtypes of depression; trials focused on depressed patients with particular symptoms such as anxious features; trials based on inpatient samples; and trials limited to patients with a particular comorbid condition such as alcoholism, anxiety disorder, or medical illness. We excluded these studies from our analysis because, by definition, they focused on limited groups of depressed patients and this would bias our findings toward suggesting that AETs are poorly generalizable.

We included only those trials focused on patients with major depression and therefore did not include trials that were based on an admixture of patients with major depression, dysthymic disorder, and minor depression. The inclusion of a small number of patients with bipolar depression was not the basis for excluding the trial from our review, though trials limited to patients with bipolar disorder were not included. Trials resulting in multiple publications based on the same sample (and the same set of inclusion and exclusion criteria) were included only once. We did not include trials of intravenous or injectable forms of medication and also did not include trials of medication combinations or augmentation strategies. We included trials whether or not the medication had received regulatory approval for the treatment of depression.

Two of the authors independently reviewed each article and completed a prespecified information extraction form listing the psychiatric inclusion and exclusion criteria used in the study. The reviewers met, compared the results of their data abstraction, and resolved discrepancies.

Statistical Analyses

We identified 170 placebo-controlled AETs published during the past 20 years. We compared the studies published during the past 5 years (2010-2014; n=56) with the studies published during the previous 15 years (n=114). The groups were compared by using the chi-square statistic, or by using the Fisher exact test if the expected value in any cell of a 2×2 table was less than 5.

RESULTS

Frequency of Psychiatric Inclusion and Exclusion Criteria Used in AETs

Table 1 lists the psychiatric inclusion and exclusion criteria that we identified in our 2002 publication, as well as 4 criteria that we did not examine in the 2002 report (previous suicide attempt, homicidal ideation and violence risk, baseline severity scale score above a maximum value, and exclusion if any Axis I disorder is present). In our previous study, we combined exclusion due to the depressive episode being either too long or too short, whereas in the present analysis, we listed these separately. Across all 170 studies, there were 6 inclusion and exclusion criteria that were used in at least half of the studies: minimum severity on a symptom severity scale (100.0%), clinically significant suicidal ideation (75.3%), psychotic features during the current episode of depression or history of psychotic disorder (84.1%), history