How Many Subjects With Major Depressive Disorder Meet Eligibility Requirements of an Antidepressant Efficacy Trial?

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Objective: To evaluate the generalizability of the results of antidepressant efficacy trials by determining how many subjects with DSM-IV major depressive disorder who apply for entry into such trials are ultimately enrolled.

Method: The screening results of 378 subjects who inquired about participating in 1 of 2 separate antidepressant efficacy trials performed at Rhode Island Hospital between 1997 and 2002 were reviewed. The number of subjects who enrolled, as well as the reasons for exclusion of those who did not meet eligibility requirements, were determined.

Results: Of the 378 inquiries, 186 subjects expressed interest and received a current major depressive disorder diagnosis. From this sample, 27 (14.5%) were ultimately enrolled in 1 of the 2 antidepressant trials. The most common reasons for exclusion were bipolar disorder (17.2%), drug or alcohol abuse (15.6%), mild depression (14.0%), medical contraindication (12.9%), and the use of prohibited psychotropic medications (12.4%).

Conclusion: The majority of subjects with major depressive disorder who apply to participate in an antidepressant efficacy trial do not meet eligibility requirements. When prescribing antidepressants, clinicians should bear in mind that the results of these trials may only be directly applicable to a small subset of patients treated in clinical practice.

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There have been increasing concerns raised recently regarding the generalizability of the results of antidepressant treatment trials, since many subjects who apply for entry into these studies do not meet eligibility requirements.[1–3] In a recent analysis of 346 patients with major depression who presented for treatment at an outpatient psychiatric practice, Zimmerman et al.[2] reported that as many as 86% would not qualify for a standard antidepressant efficacy trial. This figure was obtained by examining the clinical profile of an unselected sample of depressed patients who presented for treatment and determining how many met at least 1 of the commonly used exclusion criteria employed in antidepressant efficacy trials. Because only about 1 in 7 patients treated in clinical practice appeared to meet eligibility requirements of a standard trial, the authors concluded that the antidepressant treatment literature may not be generalizable to a large percentage of patients treated in the real world. In the present report, we sought to determine how accurate this estimate was by examining how many subjects with major depressive disorder who applied to participate in 2 separate antidepressant trials were actually excluded.

METHOD

We reviewed the screening results of 378 subjects who inquired about participating in 1 of 2 antidepressant treatment trials that were conducted at Rhode Island Hospital (Providence, R.I.) between 1997 and 2002. Both studies sought to enroll subjects who received a principal diagnosis of major depressive disorder, recurrent. One study examined a new antidepressant medication in an 8-week, double-blind, placebo-controlled trial. The other study offered treatment with 1 of 2 U.S. Food and Drug Administration–approved medications for 8 months, followed by a 2-year maintenance phase that included a placebo arm.

Subjects called in from a variety of recruitment sources (radio, newspaper advertisement, flyers, Web site, etc.). During an initial telephone screening, trained research assistants briefly explained the purpose and nature of the study being offered and answered any questions. For subjects who continued to express an interest, interviewers

then asked for a description of the problem that precipitated the call. If appropriate, interviewers administered a depression symptom checklist, developed for this study, to ensure that subjects met DSM-IV criteria for current major depressive disorder. Next, interviewers established the time line of the depressive episode, including onset and duration of illness. Finally, interviewers assessed psychiatric, medical, and substance use histories; current medications; past treatment history; presence of psychosis; and suicidality.

At any point in the interview, researchers could probe to see if the subject seemed likely to be disqualified from the study (e.g., for an unstable medical condition, substance use disorder, recent suicide attempt). Once a subject met an exclusion criterion, the screening interview would be terminated and referrals to alternative treatment facilities would be made. Most telephone screening interviews lasted one-half hour.

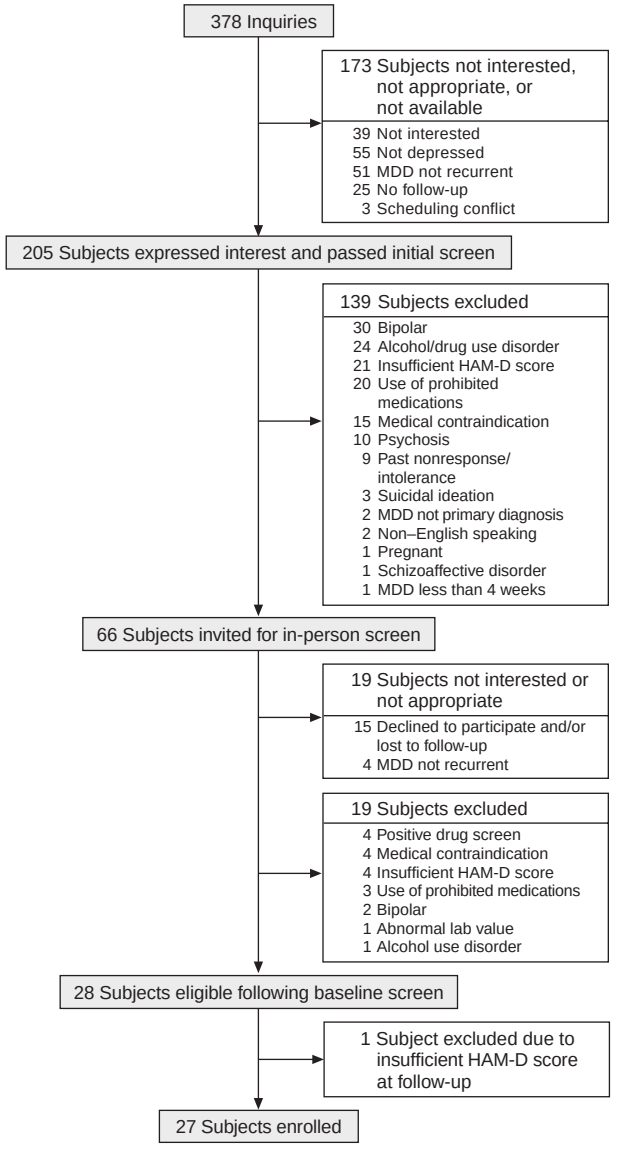
Subjects who met eligibility criteria following the telephone screening were invited to participate in an in-person interview. During this interview, written, informed consent was obtained from each subject. In addition, standardized assessments were performed including a Structured Clinical Interview for DSM-IV,[4] a Hamilton Rating Scale for Depression (HAM-D)[5] rating, and a urine drug screen. Subjects could withdraw from the study or be excluded from the study during any stage of the screening process. The number of subjects who enrolled as well as the reasons for exclusion of those who did not meet eligibility requirements were determined.

RESULTS

During the telephone screening process, 173 of the 378 subjects indicated that they were not interested, they were not available, or their depression was not recurrent. Fifteen of the remaining 205 subjects subsequently withdrew consent and 4 were found not to have recurrent depression during the in-person screening. Thus, there were 186 subjects with major depressive disorder who were interested and potentially appropriate to participate in the study. Of these, 27 (14.5%) ultimately met the eligibility requirements and were enrolled in 1 of the 2 antidepressant trials (Figure 1).

Reasons for exclusion were diagnosis of bipolar disorder (N = 32 [17.2%]), current or recent alcohol or drug abuse (N = 29 [15.6%]), insufficient HAM-D score (N = 26 [14.0%]), medical contraindication (N = 19 [10.2%]), use of prohibited ancillary psychotropic medications (N = 23 [12.4%]), presence of psychosis (N = 10 [5.4%]), past nonresponse to treatment (N = 9 [4.8%]), presence of suicidal ideation (N = 3 [1.6%]), major depressive disorder not the principal diagnosis (N = 2 [1.1%]), non–English speaking (N = 2 [1.1%]), pregnancy (N = 1 [0.5%]), diagnosis of schizoaffective disorder (N = 1 [0.5%]), abnormal laboratory value (N = 1 [0.5%]), and duration of depressive episode less than 4 weeks (N = 1 [0.5%]).

Figure 1. Combined Subject Flow From Inquiry to Enrollment of 2 Antidepressant Efficacy Trials



Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder.

DISCUSSION

Of 378 inquiries we received from subjects considering participating in 1 of 2 antidepressant efficacy trials, only 27 (7.1%) were ultimately enrolled in a trial. This illustrates one reason why it has become so difficult to recruit subjects into antidepressant trials, and why recruitment costs tend to be so high. Many of these subjects, of

course, may not have been diagnosed with major depressive disorder, while others ultimately declined to participate. Of the 186 subjects with major depressive disorder who were interested in participating, only 27 (14.5%) met eligibility requirements. Thus, 159 (85.5%) were excluded due to 1 or more of the exclusion criteria. This figure is nearly identical to the 86.0% rate of exclusion obtained by Zimmerman et al.[2] in their analysis of treatment-seeking patients. Our results, therefore, provide further confirmation that antidepressant efficacy trials may be evaluating only a small subset of patients with major depressive disorder.

Of the specific exclusion criteria used, several in particular have direct clinical implications. Approximately 1 in 6 subjects with major depressive disorder were excluded due to a history of mania or hypomania, yet the efficacy of pharmacotherapy for bipolar depression remains remarkably understudied.[6] The exclusion of subjects with mild depression is almost universal among antidepressant trials.[7] Mild depression is commonly encountered in both primary care as well as outpatient psychiatric settings, and the exclusion of these subjects means we are unable to accurately gauge how efficacious antidepressants are for mild depression. The exclusion of subjects taking ancillary psychiatric medications (usually benzodiazepines) and those with a history of nonresponse to prior antidepressant treatment likely excludes subjects with comorbid anxiety, as well as those with a history of treatment resistance, respectively—2 groups that are commonly encountered in psychiatric practice. On a positive note, our results suggest that women of childbearing age are probably well represented in antidepressant studies since few women were excluded due to pregnancy, lactation, or lack of adequate contraception, as has found by other investigators.[1]

Several limitations to the present study should be noted. First, this study was carried out entirely at 1 site. It is possible that rates of exclusion vary by site as a function of differences in screening methods. Second, our analyses were drawn from 2 antidepressant trials, of which the exclusion criteria may not necessarily be representative of other trials that are conducted. One unusual feature of these 2 trials is that subjects were not excluded due to psychiatric comorbidity other than substance use disorders. Had psychiatric comorbidity been grounds for exclusion, an even greater number of subjects would have been excluded. Thus, our estimate of the number of subjects excluded may be even lower than what would be found in other studies. Third, the screening process used to determine eligibility was designed to be efficient, and subjects who met 1 exclusion criterion were not further evaluated to determine whether other exclusion criteria also applied. Thus, rates of exclusion based on individual criteria can not be inferred from our results, except as minimum rates, because subjects may have met multiple criteria. Finally, the study designs used in the present analysis only included subjects with recurrent depression. It is unclear how subjects with recurrent major depressive disorder might differ from those experiencing their first episode, but our results may only be applicable to the former cohort.

In conclusion, our results provide further confirmation that antidepressant efficacy trials include only a small subset of the entire population of depressed patients. This does not mean that the results of antidepressant efficacy trials do not apply to the remaining populations of patients, but rather that they may not apply to certain subpopulations.

Evaluating the efficacy of antidepressant medications in the populations of patients currently excluded from antidepressant trials will be critical to better gauge the true effectiveness of currently marketed antidepressant medications.

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