Remission Rates With 3 Consecutive Antidepressant Trials: Effectiveness for Depressed Outpatients

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Objective: This effectiveness study assessed remission rates in patients who had the opportunity to receive up to 3 antidepressant trials if unresponsive.

Method: One hundred seventy-one consecutive outpatients entered 1 of 3 studies for the treatment of major depressive disorder (DSM-IV criteria) from January 1999 through December 2001. This group primarily received fluoxetine as a first treatment in trials lasting 6 to 12 weeks (a small number received gepirone). If unimproved, patients received a second or third trial (primarily clinician's choice). A standard criterion to determine remission—a score of 7 or less on the 17-item Hamilton Rating Scale for Depression—was used. In order to contrast remission rates with first-generation antidepressants, patients' outcomes in a previously published study that compared placebo, phenelzine, and imipramine were also examined (N = 420).

Results: In an intent-to-treat analysis, 66% (113/171) of patients who were treated with second-generation antidepressants and 65% (275/420) of patients who were treated with first-generation antidepressants eventually achieved remission.

Conclusions: Remission rates in the effectiveness study are approximately 20% higher than the rates usually cited, a result of our choice to examine outcome following 3 treatment trials. This choice is dictated by good clinical practice. The usual procedure when comparing treatment modalities is to assess outcome after a single antidepressant trial. The cumulative high remission rates suggest antidepressants are effective and should encourage more patients to seek treatment and physicians to develop techniques to improve patient adherence.

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Although depression has morbidity comparable to most medical disorders, half of depressed patients are untreated.[1,2] It is also incongruous that in spite of increasing use, doubts continue to be raised about antidepressants.[3–8] For example, an analysis of a U.S. Food and Drug Administration (FDA) database of 19,000 patients concluded that the symptom reduction for the newer drugs in this cohort and placebo differed by merely 10%.[4] A recent public health advisory further compromises the status of antidepressants.[9] While stating that "the FDA has not concluded these drugs cause worsening of depression or suicidality," the advisory requires that drug labeling note a possible antidepressant-suicide link.[9] Such reports may explain the media's characterization of antidepressants as not very helpful (e.g., "55 to 65 percent are not helped nearly enough . . . " side effects result in the drugs "simply not being worth the trouble"[8]). Negative media portrayal and weak efficacy studies may contribute to patients' avoidance of treatment. We suggest that the reliance on industry-sponsored studies and on measuring improvement after 1 trial has led to an inaccurate assessment of antidepressant utility.

The purpose of this article is to estimate the effectiveness of antidepressants. The Agency for Health Care Policy and Research (AHCPR) recommends at least 3 trials of different medications for unresponsive patients.[10] We could find no reports measuring outcome after 3

successive drug trials. "Effectiveness" studies differ from "efficacy" studies since they are uncontrolled, and observed improvement may not be solely attributable to drug. Effectiveness studies reflect outcome in clinical settings. Nonspecific effects, such as spontaneous remission, contribute to improvement. Effectiveness studies do suggest that a comparable patient group may exhibit equivalent improvement following a similar intervention. However, the precise proportion of improvement attributable to drug cannot be ascertained.

Difficulties associated with the use of placebo and with keeping patients and raters blinded for 3 trials make it unlikely that such a study will be done. In this article, we hope to mimic an effectiveness model using research and clinical data to approximate outcome in a clinical setting. Consistent with an effectiveness model, approximately 20% of the patients did not follow a fixed algorithm. Patients in the first sample primarily received second-generation antidepressants (4/171 received first-generation antidepressants); patients in the second sample received first-generation antidepressants. Problems associated with generalizing outcome from a tertiary treatment center to an effectiveness setting that is typically observed in primary care are described in the Discussion.

We deviate from the usual assessment of remission by measuring change after 3 treatments. The tradition is to assess the benefit following a single antidepressant trial. Outcome after a single trial inadequately reflects antidepressant benefit since an ineffective treatment would be switched in 6 to 8 weeks. This is consistent with practice in other medical specialties: failing a first treatment, a hypertensive patient would not be considered treatment-resistant.

Achieving a consensus among experts on selecting criteria defining meaningful improvement is not easy. Criteria, such as a 50% improvement in the Hamilton Rating Scale for Depression (HAM-D) score, include patients with residual symptoms. Patients who are not symptom-free are more likely to relapse and seek medical care compared to those who are asymptomatic.[11] For these reasons, we selected "remission," defined as a HAM-D score on the first 17 items of less than or equal to 7, as the criterion for improvement.[11] If a final HAM-D score was unavailable, patients were considered in remission if clinic notes suggested that they were euthymic.

Remission rates, primarily available from industry-sponsored studies, vary. For example, combined data from several studies (N of approximately 2000) suggest remission rates for venlafaxine, other antidepressants, and placebo of 45%, 35%, and 25%, respectively.[12] Similar remission rates have been reported for sertraline and imipramine in a sample of 635 patients (41% and 39%, respectively).[13] Based on such data, a recent editorial suggests that antidepressants are associated with a 50% response rate but only a 35% remission rate.[4] Data of this type would lead to the conclusion that remission rates for major depression are approximately 40% ± 5%. Reports such as these contribute to the view that antidepressants have limited efficacy.

If Patients Receive 3 Courses of Antidepressants, What Remission Rate Can Be Anticipated?

In this article, we estimate remission rates from 3 successive trials using research and clinical assessments. The Depression Evaluation Service, a research clinic at the New York State Psychiatric Institute and Columbia University, was the study site. In the initial data set (Sample 1), patients received primarily second-generation antidepressants. For each patient, the first drug trial occurred as part of a research study. For patients unresponsive to the first trial, further treatment depended on the "clinician's choice" and thus resembles a clinical setting. This explains why a fixed algorithm was not followed after the first treatment.

Outcome in Sample 1, using primarily second-generation antidepressants, is contrasted with a published study (Sample 2) comparing first-generation antidepressants (phenelzine and imipramine).[14] In the placebo-controlled imipramine and phenelzine study (Sample 2), patients unresponsive to the first medication received the second medication in successive, random, double-blind trials (details below). Patients failing to respond to placebo were switched double-blind to one of the drugs. Patients unresponsive to 2 drug trials were treated openly (treatment selected by clinician's choice). In the first patient sample, approximately 80% of the ratings were not blind (see explanation below). In contrast, in Sample 2, approximately 80% of the ratings were collected under double-blind conditions. In Sample 2, a placebo was available only during the first randomization. The hypothesis tested in Sample 2 was that a monoamine oxidase inhibitor (MAOI) would have greater efficacy than a tricyclic antidepressant (TCA) in patients with atypical depression. We believe that ratings were conservative and blind but not the equivalent if there had been placebo randomization during the second and third treatments. Thus, the group studied a decade earlier (Sample 2) may be used cautiously to calibrate the reproducibility of newer antidepressants' remission rates and to estimate how blind ratings affected outcome.

METHOD

In the first sample, a consecutive series of patients diagnosed with major depressive disorder (DSM-IV criteria) and enrolled from January 1, 1999, to December 30, 2001, were included. There were 3 ongoing studies that enrolled 171 patients in this period (outlined in Table 1). In the second sample, all patients took part in the phenelzine, imipramine, and placebo trial.[14] Outcome for the 2 samples with each of the 3 treatments appears in Figure 1.

Table 1. Outline of Studies in Sample 1 and Sample 2 of Outpatients With Depression Treated With up to 3 Drug Trials

Study	Drug	Design	Duration
Sample 1			
Study I (N = 129)			
Treatment 1	Fluoxetine	Open-label	12 wk
Treatment 2	Nonresponders to Treatment 1 received clinician's choice	Open-label	8–12 wk
Treatment 3	Nonresponders to Treatment 2 received clinician's choice	Open-label	8–12 wk
Study II (N = 27)			
Treatment 1	Gepirone, fluoxetine, placebo	Double-blind	8 wk
Treatment 2	(a) Nonresponders to fluoxetine and placebo received gepirone	Double-blind	8 wk
	(b) Nonresponders to gepirone received fluoxetine	Double-blind	8 wk
Treatment 3	Nonresponders to Treatments 1 and 2 received clinician's choice	Open-label	8–12 wk
Study III (N = 15)			
Treatment 1	Fluoxetine	Single-blind	6 wk
Treatment 2	Nonresponders to fluoxetine received imipramine	Single-blind	6 wk
Treatment 3	Nonresponders to imipramine received clinician's choice	Open-label	6 wk
Sample 2[a]			
Study I (N = 420)			
Treatment 1	Imipramine, phenelzine, placebo	Double-blind	6 wk
Treatment 2	(a) Nonresponders to placebo received imipramine or phenelzine	Double-blind	6 wk
	(b) Nonresponders to imipramine or phenelzine received the alternate drug	Double-blind	6 wk
	(c) Nonresponders to placebo in Treatment 1 who were nonresponders to imipramine or phenelzine in Treatment 2(a) received the alternate drug	Double-blind	6 wk
Treatment 3	Nonresponders to Treatment 2 received clinician's choice	Open-label	6 wk

[a]All patients in Sample 2 followed the same study design.

Sample 1: Second-Generation Antidepressants

Remission was defined as a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[15] score of less than or equal to 7.[11] Throughout this article, all HAM-D scores refer to HAM-D-17 scores. We also examined a self-rated Symptom Checklist-90 (SCL-90)[16] depression factor score as a measure of "remission."[17] For the SCL-90, remission was defined as a score within 1 standard deviation of the mean of a "well" epidemiologic community sample defined by the Psychiatric Epidemiology Research Interview (PERI).[17] The SCL-90 is used to help validate clinicians' ratings. We contrasted the proportion of patients who achieved remission status by HAM-D scores with the proportion of patients whose SCL-90 score was equivalent to the score of the well community sample, as well as computed the correlation of the 2 scores. If there is a strong correlation of clinician and patient ratings, it supports the validity of clinician ratings. This is only true if there was no patient prodrug bias (examined in the Discussion). In cases where there was no final HAM-D score or SCL-90 score, clinical charts were reviewed. The judgment "in remission" was reserved for patients who were described as "euthymic," "depression-free," or "much improved/depression-free."

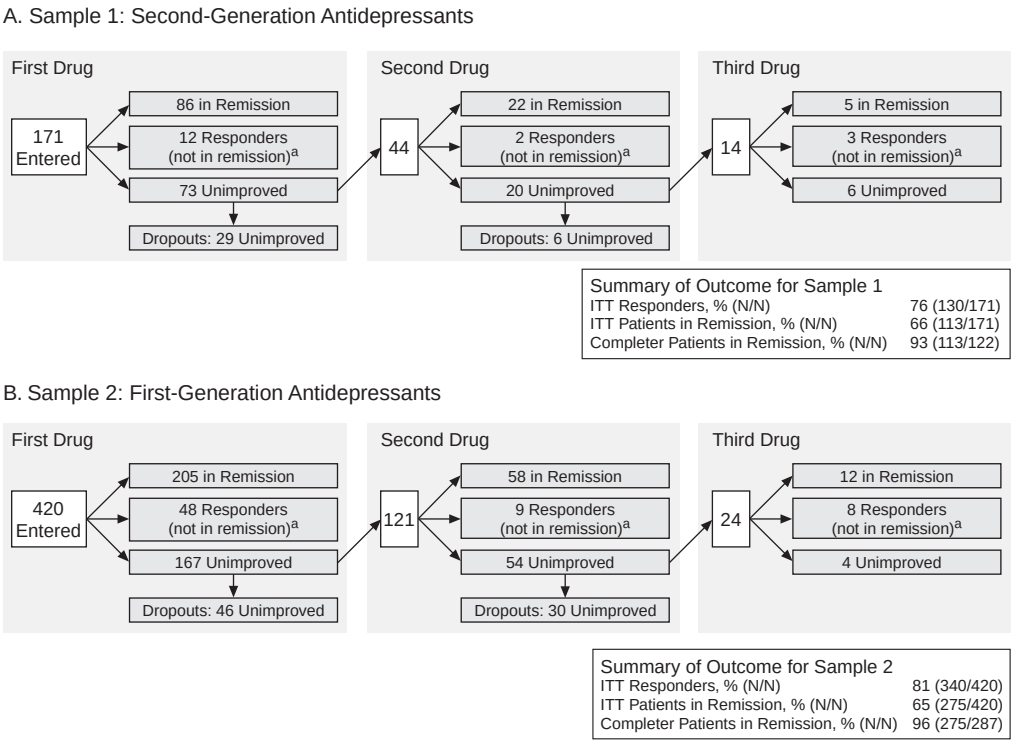
The 3 ongoing studies in 1999 to 2001 are outlined in Table 1. In a 12-week study, which examined outcome predictors during prophylactic treatment, 129 patients with major depressive disorder were treated with fluoxetine. After 12 weeks, nonresponders received open clinical treatment. A second study of 27 patients with major depressive disorder compared an experimental antidepressant, gepirone (an azapirone), with fluoxetine and placebo for 8 weeks. Patients unresponsive to placebo after 8 weeks received gepirone, as did fluoxetine nonresponders (under blind conditions). Conversely, gepirone nonresponders received fluoxetine. The third study examined the relationship of placebo response to brain laterality determined by dichotic listening.[18] Fifteen patients with major depressive disorder, dysthymia, or depression not otherwise specified received 3 consecutive treatments of 6 weeks each: first placebo, second fluoxetine, and third imipramine. Patients rated at least "much improved" did not switch treatments.

In all studies, patients were 18 to 65 years of age. Those with another Axis I diagnosis, illicit drug use in the past 3 months, or a significant medical illness were excluded. After a description of the procedures and possible side effects, informed consent was obtained. Approval for the investigations was obtained from the New York State Psychiatric Institute Institutional Review Board. Throughout the study, patients who received placebo as a first treatment and responded were removed from the analysis, and their data were not considered further.

Sample 2: First-Generation Antidepressants

Four hundred twenty patients who took part in a previously published study of placebo, phenelzine, and imipramine constitute this sample.[14] After a description of the procedure and possible side effects, informed consent was obtained. In the first phase, patients were randomly assigned to placebo, phenelzine, or imipramine for 6 weeks. Responders continued the same treatment (30 placebo responders are not discussed further). Approval for the investigation was obtained from the New York State Psychiatric Institute Institutional Review Board. In

Figure 1. Outcomes of 2 Samples of Depressed Patients Treated With up to 3 Drug Trials



[a]Received no further treatment; classified as not in remission.
Abbreviation: ITT = intent-to-treat.

Figure 1, for Sample 2, under the heading "first drug," 91 of the 420 patients are included who received placebo first, did not respond, and were randomly assigned blind to imipramine or phenelzine. Patients unresponsive to the first drug (phenelzine or imipramine) were switched double-blind to the other drug. Patients unresponsive to the 2 active drugs were offered additional treatment.

The first half of patients to enroll in Sample 2 were evaluated with the Schedule for Affective Disorders and Schizophrenia (SADS),[19] not the HAM-D. We followed the accepted method of converting SADS scores to HAM-D-17 scores.[20] This is referred to as the extracted HAM-D.

Outcome Analysis

The initial analysis included all randomly assigned patients (intention-to-treat [ITT]). Subsequent analyses were confined to patients who achieved remission or who needed and received 3 treatment courses (completers). Patients were considered in remission only if they maintained a remission status through the endpoint visit.

RESULTS

Sample 1: Estimating the Proportion in Remission

Demographic characteristics are presented in Table 2. The patient outcome is summarized in Figure 1. With the first treatment, 52% (84/163) of patients who had a final HAM-D score were rated in remission. On chart review, 25% (2/8) with missing ratings were judged in remission. Therefore, with the first treatment, 86 patients were judged in remission, 12 were responders (not in remission but received no further treatment), and 73 were not improved. Of the 73 not improved, 29 dropped out and 44 had a second treatment.

With a second drug, 9 of 20 patients with a final HAM-D score had a score in the remission range. Thirteen patients who had no final HAM-D score (most were treated openly) on chart review were judged in remission. Therefore, with a second treatment, 22 patients were in remission, 2 were responders (not in remission but received no further treatment), and 20 were not improved (6 dropped out and 14 received a third treatment). All third treatments were by clinician's choice. Fourteen patients received a third treatment; 5 were judged in remission, 3 were responders (not in remission), and 6 were not improved. Therefore, with an ITT analysis, 66% (113/171) were in remission. For completers who either remitted or received 3 treatments, 93% (113/122) were remitted.

The validity of the classification of "remission" may be examined by comparing patients' self-rated SCL-90 scores to a depression-free control group. A "well" community identified by a PERI evaluation[21] had a mean ± SD

Table 2. Demographic Characteristics of Outpatients With Depression Treated in 2 Sample Groups With up to 3 Drug Trials

Characteristic	Sample 1 (N = 171)	Sample 2 (N = 420)
Age, mean ± SD, y	35.81 ± 11.24	36.77 ± 10.48
Gender, female, % (N/N)	54 (92/171)	61 (256/420)
HAM-D-17 score, mean ± SD	16.95 ± 3.93[a]	14.10 ± 3.90[b]
Diagnosis, % (N/N)		
Chronic depression	82 (141/171)	74 (308/416)
Major depressive disorder	92 (156/170)[c]	75 (312/417)
Dysthymia	8 (14/170)	17 (64/377)
Atypical depression	78 (133/171)	82 (345/420)

[a]N = 151.
[b]N = 412.
[c]All subjects in the fluoxetine discontinuation and gepirone studies had a diagnosis of major depressive disorder (N = 156).
Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

SCL-90 depression factor score of 1.7 ± 0.58. The proportion of patients by HAM-D score criteria who met the PERI well-community standard was 90% (55/61). This high proportion supports the validity of the HAM-D ratings.

Another measure of validity is the relationship between patient and clinician ratings. The SCL-90 11-item depression subscale was correlated (Pearson correlation) to the clinician-rated HAM-D ($r = +0.79$, $p < .000$). These robust correlations support the clinician ratings' validity. Self-rating scales validate clinicians' ratings only if no patient prodrug bias exists (see Discussion).

One hundred fifty-seven patients received fluoxetine and 14 patients received gepirone as the first drug. The mean ± SD fluoxetine dose for responders was 57 ± 12 mg/day and for nonresponders was 47 ± 18 mg/day. The gepirone dose was 60 to 80 mg/day.

During the second and third treatments, there were 27 patients rated "in remission." Two patients received an MAOI (tranylcypromine 60 mg), and 2 other patients received a TCA (imipramine 275 mg/day). All others received doses of second-generation antidepressants that did not exceed the manufacturers' guidelines.

Sample 2: Estimating the Proportion in Remission

To simplify the presentation, 30 placebo responders are not discussed here. For 91 patients who were unimproved on placebo, their initial treatment is considered under the heading "First Drug" in Figure 1. Patients were randomly assigned to phenelzine or imipramine. Figure 1 includes 329 patients whose first treatment was phenelzine or imipramine and 91 patients who received placebo and were unimproved and double-blind switched to one of the active drugs. If patients were unresponsive, a switch to the other drug occurred after 6 weeks.

The patient outcome is summarized in Figure 1. With the first treatment, 53% (182/342) of patients who had a final HAM-D or SCL-90 score were rated in remission. On chart review, 77% of patients (23/30) with missing ratings were judged in remission. Therefore, with the first treatment, 205 patients were judged in remission, 48 were responders (not in remission but received no further treatment), and 167 were unimproved. Of the 167 unimproved patients, 46 dropped out and 121 received a second drug.

With a second drug, 55% (37/67) of patients who received a final HAM-D or SCL-90 score had scores in the remission range. Twenty-one patients who had a missing final rating or who were treated openly were judged in remission on chart review. Therefore, with the second treatment, 58 patients were in remission, 9 were responders (not in remission but received no further treatment), and 54 were not improved (30 patients dropped out, and 24 received a third treatment). All third treatments were selected by clinical choice. Chart review indicated that 12 patients were in remission, 8 were responders not in remission, and 4 were not improved. Therefore, with an ITT analysis, 65% (275/420) were in remission, 80% (219/275) under double-blind conditions. For completers (either patients in remission or patients who received 3 treatments), 96% (275/287) remitted.

If only less ill patients completed the SCL-90, the proportion of SCL-90 scores meeting remission criteria would be inflated. The HAM-D scores of patients who were responders with and without an SCL-90 score were equivalent ($t = 0.65$, $df = 108$, $p = .52$). This indicates that less ill patients were not the only patient group to complete the SCL-90. The high correlation between the SCL-90 depression factor and the HAM-D-17 ($r = +0.78$, $p = .001$) supports the validity of the clinicians' ratings.

In the double-blind portion of the study, mean ± SD dose of imipramine was 255 ± 69 mg/day and for phenelzine was 76 ± 23 mg/day. The third treatment most commonly used was an MAOI combined either with a TCA, lithium, or a stimulant. Doses did not exceed the manufacturer's suggested maximum dose.

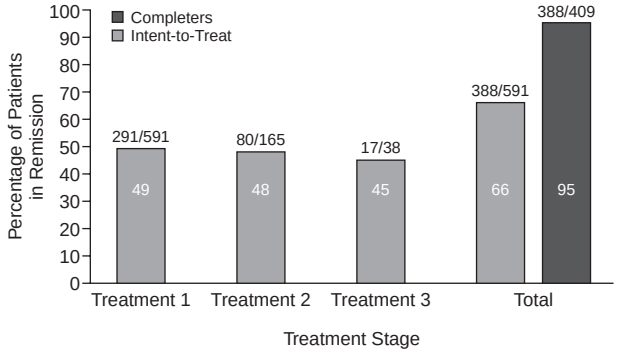
In summary, 208 patients who had a HAM-D score of less than or equal to 7, 11 patients who had SCL-90 scores within 1 standard deviation of the community mean (but had no final HAM-D score), 44 patients who dropped out of the formal drug protocol and were treated openly, and 12 patients who failed to respond to 2 drugs under double-blind conditions and had a third treatment achieved remission status (the 44 patients and 12 patients who had a clinical chart evaluation but no HAM-D scores or SCL-90 ratings available). Therefore, 65% (275/420) of the patients were judged in remission.

The outcome for Sample 1 and Sample 2 is summarized in Figure 2.

DISCUSSION

Our salient finding is that most depressed patients who remain in treatment benefit. In an ITT analysis, in both

Figure 2. Proportion of Intent-to-Treat Patients in Remission and Completers in Remission[a,b]



[a]Sample 1 (N = 171) and Sample 2 (N = 420) combined (N = 591).
[b]For the percentages shown, the numerator is the number in remission for both samples, and the denominator is the number for both samples who received a new treatment during that period. For example, 165 patients (44 + 121) received a second drug and 80 patients (58 + 22) remitted. Therefore, 48% (80/165) remitted with Treatment 2.

combined samples, 66% achieved remission. Approximately 95% of patients receiving 3 trials achieved remission. Approximately 5% of patients were in an intermediate state (HAM-D score of 8 or 9) and are not included in the "remission" group, even though much improved. Therefore, the 66% remission rate may be the estimate's lower bound of meaningful clinical improvement, and the rate may be closer to 70%. Since this is an effectiveness study, the improvement attributable to a specific drug effect is not quantifiable. Since this group of patients is predominantly chronically depressed, we suspect that spontaneous remission does not explain the majority of the improvement.

Because there is no follow-up in this study, we do not know how long these remissions lasted. Other limitations include the fact that formal blind ratings were not completed during all 3 courses of treatment. However, 80% (219/275) of patients achieving remission in Sample 2 had blind ratings. Placebo was utilized during the first 6-week trial of this study, and subsequent "blind" comparisons contrasted 2 drugs. This is not the equivalent of a placebo throughout the study. The ratings' validity does gain support from the high correlation between patient self-ratings and doctors' ratings, as well as the high proportion achieving remitter status using the "well-community sample" as a cutoff.

If there is a bias for patients to over-report improvement while on drug treatment, both clinician and patient could be reliable but overestimate remission rates. The low placebo response rate (22%–29%) that was found in a pooled analysis of patients treated with active placebo suggests that patient prodrug bias is unlikely since side effects did not increase remission rates on placebo.[22]

The assessment that antidepressants are marginally effective may be explained by the data utilized to measure efficacy and the definition of "adequate antidepressant treatment."[2–6] First, we examine problems with the data. Assessments of effect size primarily rely on studies funded by pharmaceutical companies. As noted in this article's introduction, in a sample of 19,000 patients submitted to attain new drug approval, specific beneficial effects exceed placebo by 10%.[4]

We suggest that these sort of data are misleading, and this is attributable to the New Drug Application (NDA) process. In the final NDA phase, pivotal, randomized placebo-controlled blinded studies are completed. These industry-funded "efficacy studies" are influenced by a desire to maximize the period of patent-dictated market exclusivity. The industries' self-selected timetable to complete the NDA may not permit adequate study of parameters such as dose and duration. A compromised study design may result.[21] Furthermore, most industry-sponsored studies have utilized multiple sites, and it is unlikely that criteria are uniformly applied. This is another source of variance. These pharma-pivotal studies may not permit accurate effect size estimates (i.e., estimates of the difference in outcome between drug and placebo).

Another salient finding is a remission rate 20% to 30% higher than the one usually cited.[5] Usually, remission rates cite outcome after 1 trial. Obviously, higher remission rates are related to the decision to consider 3 antidepressant trials as appropriate treatment.

We found only 1 study with 2 active treatments in which patients failing to respond to 1 drug were systematically treated with another.[13,23] Patients were randomly assigned to sertraline or imipramine treatment, and nonresponders to the first drug received the second drug. From the published data, it appears that in the ITT analysis, 40% remitted, but approximately 60% (248/415) who had 2 trials achieved remission. Differences between the present report and the sertraline–imipramine trial include the lack of a third drug trial and multiple study sites, which are generally associated with less uniform treatment.

Is a similar outcome attainable in effectiveness settings? In the present study, clinicians had broad experience treating depressed patients and greater time flexibility with patients compared to the usual primary care setting. The AHCPR recommends visits every 1 to 2 weeks to monitor medication and educate and support patients for at least 6 weeks.[10] This is rarely feasible in primary care settings. Therefore, the greater time, flexibility, and research training probably increased the proportion of patients in remission.

Another consideration is sample selection. We excluded patients over age 65 and with concurrent medical or psychiatric disorders, as well as those with mild or very severe depression. Inclusion of patients with these characteristics would lower remission rates.[7]

Antidepressant selection or combinations of medications may also differ in primary care and tertiary care sites. However, in Sample 1, most patients were treated with widely used drugs: primarily a selective serotonin reuptake inhibitor, bupropion, and venlafaxine. In the third treatment phase of Sample 1, only 2 patients received an MAOI. If basic guidelines are followed, rapport is established, and treatment length and dose are appropriate, then results similar to ours may be obtained in most settings. In spite of this approach, an approximately 30% dropout rate was observed. Approaches to reduce this rate need to be developed since some patients unresponsive or intolerant to one drug may benefit from another.[24] Emphasizing the potential necessity of multiple treatments and using approaches to enhance adherence might minimize patient dropout. Improving adherence rates should improve the remission rate.

A large collaborative study is currently being conducted that will provide data on outcome with controlled consecutive clinical trials.[4] Our data suggest that correctly diagnosed depressed patients who receive 3 adequate trials of antidepressant medication have an approximately 90% chance of achieving a state of remission. We could find no systematic analysis of why patients leave treatment. A major challenge is motivating depressed patients to continue treatment.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Lithobid, Eskalith, and others), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

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