The Treatment of Chronic Depression, Part 1:

Study Design and Rationale for Evaluating the Comparative Efficacy of Sertraline and Imipramine as Acute, Crossover, Continuation, and Maintenance Phase Therapies

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Background: Chronic depressions are common, disabling, and undertreated, and prior chronicity predicts future chronicity. However, few studies directly inform the acute or maintenance phase treatments of chronic depressions and even less is known about the effects of treatment on psychosocial functioning.

Method: We describe the design and rationale for 2 parallel double-blind, randomized, multicenter acute and maintenance phase treatment trials. One focused on DSM-III-R major depression currently in a chronic (≥ 2 years) major depressive episode, the other on DSM-III-R major depression with concurrent DSM-III-R dysthymia ("double depression").

Results: Considering the critical knowledge deficits, we designed a 12-week acute phase safety and efficacy trial of sertraline versus imipramine, followed by a 16-week continuation treatment phase for subjects with a satisfactory therapeutic response. Patients receiving sertraline who successfully completed the continuation phase entered a 76-week maintenance trial to compare sertraline with placebo; those taking imipramine continued without a placebo substitution. As part of the acute trial, subjects completing but failing to respond to the initial 12-week acute phase medication were crossed over (double-blind) to the alternative medication for a 12-week acute phase trial. We obtained naturalistic follow-up data (up to 18 months) for subjects exiting the protocol at any time.

Conclusion: Multiphase protocols for chronic depression can test efficacy by randomized contrasts as well as shed light on key clinical issues such as the degree of response or attrition expected at particular times in a trial or the preferred medication sequence in a potential multistep treatment program.

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This article presents the rationale, design, and procedures for 2 double-blind, randomized, multicenter treatment trials that enrolled subjects with 2 forms of chronic depression in parallel, identical protocols. The 2 forms of depression were (1) DSM-III-R major depression currently in a chronic (≥ 2 years) major depressive episode, and (2) major depression with concurrent DSM-III-R dysthymia currently in a major depressive episode ("double depression"). These 2 trials compared the safety and efficacy of sertraline and imipramine in acute and continuation treatment and subsequently compared sertraline with placebo in maintenance treatment. Subjects who completed but failed to respond to 12 weeks of acute phase treatment were eligible to cross over (double-blind) to the alternative acute phase medication. In addition, we obtained naturalistic follow-up data for 18 months for subjects exiting the protocols at any time.

These protocols were designed and nested together to test a priori hypotheses as well as to provide important descriptive information in this vastly understudied area. The 2 companion articles in this issue report on acute phase efficacy and safety findings, and the effects of acute phase treatment on psychosocial functioning. A third article (published elsewhere) reports results of the 18-month maintenance phase.[1] Subsequent reports will provide other results from this multiphase study.

WHY STUDY CHRONIC DEPRESSIONS?

Chronic Depressions Are Common

Major depression often has a chronic or recurrent course with incomplete symptomatic and psychosocial recovery interepisode.[2–9] Rates of chronicity for naturalistically treated depressive episodes reportedly range from 7% to 12% after 5 to 10 years of prospective follow-up.[3,4] Among patients who do respond to treatment or who spontaneously remit, many suffer subsequent relapses or recurrences or both.

Dysthymia, another form of chronic depression lasting at least 2 years, is also common. Community studies reveal a point prevalence of about 2% to 3%.[10,11] Among psychiatric outpatients, the prevalence of dysthymia is high (26% to 36%).[7]

Among inpatients with major depression, chronic depressions persisting through decades of follow-up occur at a rate of 7% to 20%.[12]

Chronic Depressions Are Particularly Disabling

Mood disorders in general[13–16] and chronic mood disorders in particular[17–19] are associated with significantly impaired functioning (e.g., work, social, family, and marital roles), lower quality of life, and increased health care utilization. Functional impairment is more severe and improves less over time with major and minor depression than in many chronic medical disorders (e.g., hypertension, diabetes mellitus, arthritis).[17,18] Lower levels of psychosocial functioning, in turn, are associated with a worse prognosis for recovery from a major depressive episode.[17,20–22] Finally, while improved psychosocial functioning is associated with symptomatic improvement in acute major depressive episodes,[14,23] less is known about psychosocial functioning in subjects with chronic depression.[24–26]

Chronic Depressions Are Undertreated

Undertreatment of all forms of depression appears to be the norm,[27–32] with rates of adequate treatment estimated to be only 10% to 40%.[30,31] Not surprisingly, patients with lower treatment rates tended to be ill longer.[33–38]

Prior Chronicity Predicts Future Chronicity

In the National Institute of Mental Health naturalistic prospective Collaborative Depression Study (CDS) cohort, only 18% of those still suffering from depression after 1 year remitted between years 1 and 5. Of the CDS subjects whose unipolar major depression remitted, over 60% had a relapse or recurrence within 5 years[39] and over 70% had a relapse or recurrence over the 10-year follow-up period (Keller et al., written communication, 1997). The risk of developing a chronic depression persisted. Approximately 25% of subjects with a relapse or recurrence did not recover within 1 year of the start of the new episode, about the same as the proportion of the original cohort who failed to recover from the index episode within 1 year.[40] Other studies suggest that chronic depressions persist in part because treatment response rates are lower after an episode has lasted 2 or more years.[41–43]

The CDS also revealed that one quarter of subjects in a chronic affective episode (major depression, mania, or schizoaffective disorder present for ≥ 2 years at study entry) never experienced at least 2 symptom-free months during the 5-year follow-up.[2] Longer duration and greater severity of the index episode, a history of nonaffective psychiatric disorders, low family income, and marital status (married) are associated with chronicity.[44,45]

Furthermore, most episodes of double depression ended with a return to the dysthymic state, although major depressive episodes occurring in the context of "dysthymia" ended sooner than did isolated major depressive episodes.[46] Only 39% of subjects with double depression remitted from both the major depressive episode and dysthymia in the first 2 years of follow-up. Additionally, a significantly higher proportion of subjects with double depression relapsed into a full major depressive episode during the following 2 years than subjects with a major depressive episode alone.[46] Residual depressive symptoms following a major depressive episode have been associated with increased risk of subsequent major depressive episodes.[46–48]

Efficacy Studies of Chronic Depression Are Uncommon

Literature reviews suggest that there has been inadequate study of chronic depression.[49] There have been only a handful of acute phase trials,[24,50–53] and only 1 randomized comparative maintenance phase trial of chronic depression,[54] although several maintenance phase trials of imipramine in recurrent depressions are available.[55–60] There are no maintenance trials of selective serotonin reuptake inhibitors (SSRIs) in chronic depression. The stark fact is that treatments for the most chronic and disabling forms of depression have not been well evaluated in efficacy trials.

QUESTIONS ADDRESSED BY THE CURRENT PROTOCOLS

What Is the Comparative Acute Phase Efficacy of Sertraline and Imipramine in Chronic Depression?

For both acute and continuation phase treatment, we tested the null hypothesis that sertraline does not differ in safety or efficacy (measured by response and remission rates) from a standard tricyclic, in this case, imipramine. Imipramine was chosen for this study because of evidence of efficacy in maintenance treatment of recurrent depressions, its role as a "gold standard" in acute treatment of nonchronic depressions, and evidence of efficacy of desipramine in acute and maintenance phase therapy of chronic depression.[36]

When Does Response Occur in Acute Phase Treatment?

Because of suggestive evidence[61–66] that chronically depressed subjects may require longer to respond than the less chronically ill, we set the duration of acute phase treatment at 12 weeks.

Do Those Responding Acutely Maintain Their Response?

Subjects responding to acute phase treatment continued on the same medication during a 16-week, double-blind continuation phase, which allowed us to determine whether subjects who had at least a satisfactory therapeutic response (without remission) after 12 weeks of treatment sustained the improvement during continuation therapy. Beyond assessing the comparative efficacy of sertraline and imipramine to prevent relapse, the continuation phase also permitted comparisons of durability of complete remission, the need for further dosage titration, and the likelihood of further improvements among partially remitted patients.

Does Switching to a Different Medication Class Result in Response for Those Failing the Initial Medication?

How to treat depressed subjects who fail to respond to initial treatment remains an understudied question.[30,67] Therefore, we also investigated whether subjects with an unsatisfactory response to 12 weeks of treatment with the initial medication would respond to the alternative medication in a 12-week, double-blind crossover trial. The crossover arm allowed us to compare the initial responders and crossover subjects with regard to depressive symptoms, psychosocial functioning, and medication tolerability during both acute and continuation phases of treatment. Those responding to the crossover were allowed to enter maintenance treatment.

Is Maintenance Phase Sertraline Effective?

Only acute phase responders who continued to benefit from continuation phase treatment were eligible to enter the maintenance trial. Twice as many subjects were randomized to sertraline as to imipramine in the acute phase to provide a sufficiently large sample to allow us to test the hypotheses that sertraline is more effective than a placebo in preventing reemergence of depression and recurrence in each of the 2 forms of chronic depression during an 18-month maintenance trial (see below). A similar question might have been posed for imipramine maintenance, but cost and feasibility considerations precluded enrolling an initial sample large enough for maintenance phase randomization to imipramine or placebo, and a previous study has established efficacy of desipramine maintenance therapy in chronic depression.[36]

Subjects who discontinued from any study phase were followed in an 18-month naturalistic follow-up study. This follow-up study was intended to provide additional data on the course of chronic depression, with treatment uncontrolled. Assessments were conducted every 6 months with the same battery of assessments included in the maintenance study.

Do These 2 Forms of Chronic Depression Differ in Their Pharmacologic Response?

By conducting 2 parallel studies, 1 for each form of chronic depression, we could address several other questions: Do times to response or to remission differ between subjects with chronic major and double depression? Do the 2 kinds of chronic depression differ in their likelihood of acute phase treatment response, in their response to crossover medication, in their continuation phase stability on each medication, or in the comparative benefit of sertraline versus placebo during maintenance phase treatment?

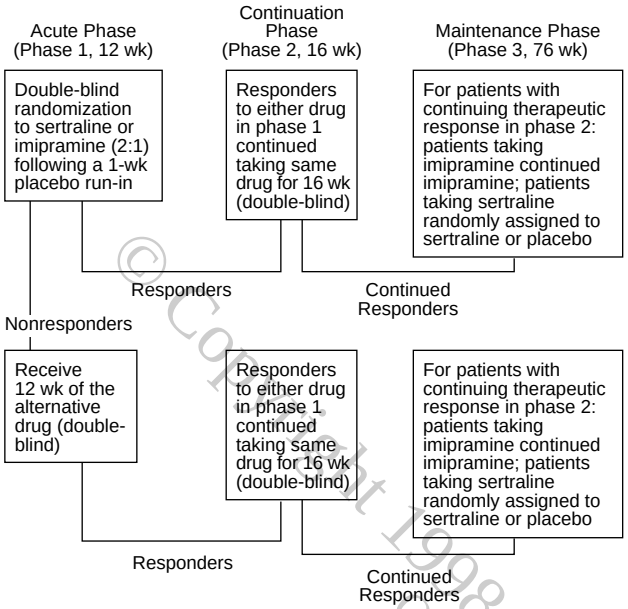
Finally, do these 2 forms of depression differ in the timing of or degree of improvement in psychosocial functioning at the time of symptomatic response or remission? What is the immediate and long-term relationship between symptomatic and psychosocial improvement in each form of depression? Does psychosocial functioning improve further during the continuation or maintenance phases of treatment for either or both forms of chronic depression?

Secondary Analyses to Refine Hypotheses for Subsequent Study

The paucity of information regarding treatment and response in chronic depression raised additional questions to be addressed in secondary analyses. One area of inquiry is predictors of outcome: Does the acute phase response rate to either medication differ by gender? Does it differ for those subjects with baseline personality disorders, greater anxiety or other Axis I or II comorbidity, or a history of alcohol or substance abuse?

In summary, the main objectives of this study were to compare the safety and efficacy of sertraline and imipramine in acute and continuation phase treatment, and to

Figure 1. Two Parallel Studies: Double Depression (N = 341) and Chronic Major Depression (N = 294)*



*During all phases, patients who withdrew or completed the study had the option of being followed in a prospective, naturalistic fashion for 18 months at 6-month intervals.

compare sertraline with placebo in preventing recurrences during an 18-month maintenance trial. In addition, the double-blind crossover treatment for those tolerating but not responding to the initial medication; the repeated multidimensional assessments during acute, continuation, and maintenance phases; and the assessments during the post-maintenance follow-up period allowed us to address clinically relevant questions with descriptive data (Figure 1).

CRITICAL DESIGN ISSUES

Why Not Use a Placebo?

We decided not to include a placebo arm in the study's acute phase for several reasons. First, we expected a placebo might lead to a high dropout rate over 12 weeks. In addition, chronicity of major depression is associated with low placebo response rates.[24,53] Third, our primary focus was on maintenance phase treatment. To require a placebo in the acute phase would most likely reduce generalizability (i.e., many patients would refuse to participate in the study).

Why Use Imipramine as a Comparison With Sertraline?

Imipramine is the best-studied medication in maintenance phase trials and has demonstrated efficacy in the long-term prevention of recurrence in major depression.[22,36,55,68–70] When compared with placebo, sertraline has demonstrated continuation phase efficacy for 1 year in the prevention of relapse in major depression.[71]

Why Is the Acute Phase Trial 3 Months in Length?

Optimal pharmacotherapy responses frequently evolve over 6, 8, or even 12 weeks.[48,72] Some evidence suggests that chronic depressions respond more slowly than acute depressions.[41,42] A 12-week acute phase protocol thus permits a comparison of nearly optimal acute phase pharmacotherapy outcomes for these chronically depressed patients, and it most likely lowers the probability of retaining placebo responders.[73]

How Is Dosing Managed?

Subjects were randomly assigned to double-blind treatment with sertraline or imipramine in a 2:1 ratio, with weekly return visits for the first 6 weeks of acute phase treatment. Visits were every 2 weeks for the final 6 weeks of acute phase treatment. The choice of doses was influenced by several factors: (1) the goal to retain as many subjects as possible, (2) the need to mirror common clinical practice, and (3) the need to ensure that each patient had an optimal opportunity to respond to each treatment. Consequently, the dosing schedule for sertraline was for weeks 1–3, 50 mg/day; then, weekly titration in 50-mg/day increments, as indicated by clinical response and side effects, to a maximum daily dose of 200 mg. The dosing schedule for imipramine was 50 mg/day (week 1), 100 mg/day (week 2), 150 mg/day (week 3), then weekly titration in 50-mg/day increments, as indicated by clinical response and side effects, to a maximum daily dose of 300 mg. Doses could be decreased at any time because of adverse experiences. The minimum doses necessary to continue in the study were sertraline, 50 mg/day, and imipramine, 50 mg/day, because efficacy data for lower doses do not exist.

To obtain maximal benefit for each subject, we defined continuation and maintenance phase doses of both medications as those that were effective in the acute phase.

How to Measure Outcomes?

At baseline, we assessed subjects' demographic features. At day 1 of washout, the Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P)[74] was performed to assess Axis I disorders, and the SCID-II,[75] the Diagnostic Interview for Depressive Personality,[76] and the Schneiderian Traits Questionnaire[77] were completed to assess possible Axis II personality disorders. A certified rater (usually a master's level nurse or clinical social worker) conducted both interviews. A psychiatrist or psychologist (with doctorate) also saw the patient to check the SCID-P and SCID-II findings and render final Axis I and II diagnoses. Family history was obtained with the Family History-Research Diagnostic Criteria.[78]

Standard outcome measures were used to evaluate symptom severity. We used the 24-item Hamilton Rating

Scale for Depression (HAM-D)[79,80] (baseline, weeks 1, 2, 4, 6, 8, 10, 12) and the Clinical Global Impressions (CGI),[81] including both the Severity of Illness (CGI-S) and Improvement (CGI-I) subscales (all visits), as the primary measures of symptomatic outcome. Confirmatory symptom outcome measures included the Montgomery-Asberg Depression Rating Scale[82] (administered with the HAM-D), the Cornell Dysthymia Rating Scale[83] (baseline, weeks 2, 4, 6, 8, 12), and the 21-item Beck Depression Inventory[84,85] (baseline, weeks 4 and 12). All symptom measures evaluated the most recent 7-day period.

Measuring psychosocial function is complex. We decided to use several measures at baseline and at weeks 4 and 12 and to include both clinician and self-rated assessments. They included the Quality of Life Enjoyment and Satisfaction Questionnaire,[86] the self-rated Social Adjustment Scale,[87] patients' global self-evaluation (using the Patient Global Evaluation), the 36-item Medical Outcome Study Health Status Questionnaire,[16] and the Global Assessment of Functioning Scale.[88] The Longitudinal Interval Follow-Up Evaluation[89] and the Endicott Work Productivity Scale[90] were administered at baseline and week 12.

How Were Ratings Made Reliable?

To ensure consistent protocol implementation, each site used the same detailed operating manual and participated in teleconferences every 2 weeks. All sites participated in investigator meetings that included training in the use of rating scales and consensus rating exercises. Raters also received on-site training for the SCID and the HAM-D. When on-site supervisors considered a rater adequately trained, videotapes of 2 SCID and 2 HAM-D interviews were submitted for review by an experienced independent rater certification group (Department of Psychiatry, Columbia University, New York, N.Y.). The expert raters evaluated the site rater's interview performance, diagnostic skills, and scale ratings. The experts compared their independent ratings and diagnoses with those of the site rater and prepared detailed critiques. If satisfied, the expert raters certified the site rater as qualified to perform interviews and ratings. Raters were certified for the SCID and the HAM-D independently. To minimize bias or pressure from the sites during rater certification, the certifying expert raters were known only to W.H. Every attempt was made to have the same certified rater see a given subject at each visit. In the absence of the designated rater, ratings were completed by an associate with whom interrater reliability had been established.

How to Define Response?

We had to define response at the end of acute phase treatment to decide whether to enter a patient into continuation phase treatment. This decision attempted to balance entering only those with a full symptomatic remission against entering those with partial acute treatment benefits who might be better served by alternative treatments. Recall also, those with an unsatisfactory acute phase response were candidates for crossing over to the alternative acute phase medication.

To address this tension, we decided to approximate clinical practice, wherein physicians usually decide that those who should continue have had either a dramatic or a substantial benefit from acute phase treatment. We operationalized the decision as follows. We defined a *remission* as a 24-item HAM-D score of ≤ 7 and CGI-I score of 1 or 2 (very much or much improved) at 2 consecutive ratings at least 2 weeks apart. This definition is a rather stringent criterion for remission.[1] A *satisfactory therapeutic response* was defined as (1) a total HAM-D score of ≤ 15, (2) a total HAM-D score decrease of ≥ 50% from baseline, (3) a CGI-S score of ≤ 3 (i.e., no more than mild depression), and (4) a CGI-I score of 1 or 2 (very much or much improved) at 2 consecutive ratings at least 2 weeks apart (see, for example, Prien et al.[91]). *Nonresponse* was defined as failure to meet criteria for satisfactory therapeutic response.

The week-12 visit served as the baseline for continuation phase treatment. Subjects who first met remission or satisfactory response criteria at week 12 were followed to week 14 and rerated. If they continued to meet criteria, they entered the continuation phase. If not, they were either crossed over to the alternative medication (if they wished) or dropped from the study.

CONTINUATION AND MAINTENANCE PHASES

Management Issues

Subjects completing acute phase therapy with at least a satisfactory therapeutic response and providing written informed consent were continued on the same double-blind medication dose for an additional 16 weeks. During continuation phase therapy, doses could be decreased for adverse experiences or increased because of insufficient clinical response by 50 mg/day per week, but the allowed dose ranges remained 50 to 200 mg/day of sertraline and 50 to 300 mg/day of imipramine.

After 16 weeks of continuation phase treatment, subjects who continued to manifest at least a satisfactory therapeutic response were eligible to enter the 76-week maintenance phase study. Subjects remained in the maintenance study until the end of the study or until they were discontinued because of recurrence.

Subjects taking sertraline were stratified for high or low probability of recurrence of depression and were randomly assigned to double-blind treatment with either sertraline or placebo. Obviously, if randomization without this stratification had resulted in a differential loading of those more likely to relapse into either sertraline or placebo, the study results could not have been interpreted with certainty.

A high probability of recurrence was defined as (1) presence of residual depressive symptomatology at the end of the continuation study (a 24-item HAM-D score ≥ 10 and CGI-S score ≥ 3) or (2) a history of 3 or more prior episodes of major depression, including the index episode. In each stratum, half the subjects were assigned to sertraline, half to placebo.

Subjects assigned to discontinue sertraline underwent dose tapering, on a double-blind basis, over a 2- to 3-week period, depending on dose. Sertraline doses were reduced by a maximum of 50 mg/week in order to minimize the likelihood of symptom exacerbation with abrupt discontinuation.

Responders to the acute phase crossover trial and subsequent continuation phase treatment were eligible for the same maintenance phase procedures. Because crossover subjects and those not requiring crossover treatment might differ with regard to the efficacy of maintenance treatment, data from crossover subjects entering the maintenance phase were analyzed separately.

How Are Depressive Symptom Exacerbation and Recurrences Defined?

The criteria for declaring a recurrence during maintenance phase treatment must balance refraining from labeling brief symptomatic worsenings as "true recurrences," since these would not, in practice, lead to a change in type of treatment, against endangering subjects by establishing such a high threshold for declaring a recurrence that unnecessary pain and suffering occur. Again, we attempted to approximate clinical practice in defining recurrence and to increase clinical monitoring when symptom worsening short of a recurrence occurred.

Subjects were assessed at each scheduled visit for recurrence of major depression. Recurrence was defined as meeting the following criteria at 2 consecutive evaluations at least 1 week apart: (1) has met DSM-III-R criteria for major depression for ≥ 3 weeks at the first evaluation and ≥ 4 weeks at the second evaluation, (2) CGI-S score of ≥ 4 (moderate or greater severity), (3) CGI-I score of ≥ 3 (minimally improved or less) from baseline of the acute phase study, and (4) HAM-D score increase of ≥ 4 points compared with score at entry to the maintenance study. Declaring a recurrence also required at least 1 concurring independent assessment by a principal investigator or senior coinvestigator, blind to medication type, dose, and side effects.

Subjects were advised to call their study physician if they experienced increased depressive symptoms that persisted for at least 1 week, and a visit was then scheduled within 1 week. Subjects who reported an exacerbation of depression, had a clinically meaningful increase in depressive symptoms, or met DSM-III-R criteria for major depression at any scheduled assessment visit were assessed for recurrence. If subjects met recurrence criteria, they were given the option to withdraw from the study.

If the subject did not meet criteria for recurrence and was not taking the maximum allowable daily dose, then, in the absence of dose-limiting side effects, the physician increased the dose, but by no more than 50 mg/day per week.

Subjects were scheduled for another visit 1 week after the dose increase. A maximum of 4 visits to adjust the dose and reevaluate the subject's clinical response was permitted. If the subject had a satisfactory response and did not meet criteria for recurrence, the subject continued in the study taking the increased dose (if the dose was increased) and was seen monthly. Subjects who were at the maximum permitted dose of sertraline or imipramine or who had dose-limiting side effects were reevaluated weekly for recurrence criteria for a maximum of 4 visits.

BREAKING THE DOUBLE-BLIND

During the maintenance phase, concerns were raised about the management of subjects experiencing a profound increase in symptoms or a formal recurrence, and the need to make medication decisions quickly. A novel statistical method was employed for unblinding patients who experienced recurrence or clinically significant worsening of symptoms. For such patients, knowledge of their treatment assignment was essential for subsequent (off-study) treatment. However, knowing the assignments of a series of patients could increase the ability of an investigator to guess the assignments of patients still in the study. A double-blind can be viewed as a continuum, with absence of knowledge regarding treatment assignment at one extreme (complete blinding) to full knowledge at the other (complete unblinding). It is along this spectrum that the integrity of the blind can be weighed against the best interests of the patient.

In consultation with FDA personnel, the sponsor's statistician monitored the ability of each investigator to guess the treatment assignment of their patients still in the study. When breaking the blind for any patient, the statistician (R.J.M.) examined the effect of unblinding on our ability to guess treatment assignment for the remaining patients at that site (before the next relapse/recurrence occurred). If any of these probabilities attained or exceeded 75%, the site agreed to refer all subsequent relapsers to a third party for treatment.

These calculations relied on the number of patients taking imipramine, sertraline, and placebo at each site. Since these numbers were random, depending on the response and discontinuation rates in the continuation study, a Bayesian approach was adopted. A prior distribution over the number of patients was specified according to clinical expectations of discontinuation and response in the continuation study. From this prior distribution, a pos-

terior distribution, conditional on the treatment assignments of the unblinded patients, was calculated, and posterior means were used to determine the randomization probabilities.

CONCLUSION

To our knowledge, these are the first randomized, double-blind, acute, crossover, continuation, and maintenance phase studies comparing an SSRI (sertraline) with a tricyclic antidepressant (imipramine) in the treatment of chronic major and double depressions. Study results will further inform clinical decisions with respect to both acute and longer term treatment of these depressions.

Drug names: desipramine (Norpramin and others), imipramine (Tofranil and others), sertraline (Zoloft).

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