A. Specific Aims

We plan to conduct a three-site comparative outcome/maintenance study to determine whether combining antidepressant medications (ADM) and cognitive therapy (CT) is more effective in the treatment of depression than ADM alone. In particular, we are interested in whether adding CT to ADM can reduce the risk of recurrence following treatment termination.

We plan to identify a sample of 450 depressed non-bipolar, non-psychotic outpatients (150 at each of three sites) and randomly assign them to either ADM alone or the combination of ADM plus CT. All patients will be treated to remission during an acute treatment phase that can last up to 18 months and involve up to four different medications, plus augmentation with lithium. Remitted patients will be kept on continuation medications for up to 12 months until fully recovered, with CT continued in the combined condition as clinically indicated. Patients who meet criteria for recovery (defined as going as additional six months without relapse beyond the point of remission) will be withdrawn from any ongoing CT and randomly assigned to one of two conditions: (a) maintenance medications; or (b) withdrawal from all pills. All patients will then be followed for the next three years.

Our specific aim is to compare ADM with the combined treatment, in order to determine whether:

- adding CT enhances the effects of ADM during initial treatment, as indexed by the rate and probability of remission and recovery;
- prior exposure to CT reduces risk for recurrence following treatment termination as indexed by reduced rates of recurrence during a subsequent three year maintenance/follow-up phase;
- differential effects associated with CT are more pronounced for patients with severe and chronic depressions, as well as depressions superimposed on long-standing personality disorders; and
- the enduring effects for CT are mediated either by changes in cognitive schemas or the acquisition of compensatory cognitive skills.

B. Background and Significance

1. Recurrent depression and the importance of prevention. Clinical depression is one of the most prevalent psychiatric disorders. It has been estimated that at least 10% of the general population will meet criterion for a major mood disorder at some time.[1] Between 50-85% of these individuals will experience multiple episodes,[2] with a significant minority experiencing three or more.[3] Clearly, stable vulnerability factors must exist that place certain individuals at elevated risk. Further, depression tends not only to be recurrent, it is also typically self-limiting. Although a minority of patients will exhibit a chronic course, most will recover from any given episode, even without treatment. Remission may be facilitated by treatment, but most patients remain at elevated risk regardless of whether recovery is spontaneous or treatment-induced. Against this backdrop, a case can be made that a treatment's capacity to reduce risk following recovery is at least as important as its ability to treat the current episode. Further, insofar as the mechanisms that mediate subsequent risk correspond to those that contribute to the initial onset of the disorder, their study should contribute to our understanding of the etiology of depression and facilitate the development of primary prevention strategies (see Hollon, DeRubeis, & Seligman, 1992, in Appendix 1).[4]

2. Antidepressant medication in the treatment of depression. Over the last four decades, the antidepressant medications have been established as the standard of treatment for the affective disorders.[5] Moreover, real strides have been made in this regard in the last few years. Pharmacological treatment has become more practical, as drugs with fewer side effects have been developed, augmentation strategies have been added,[6,7] and extended treatment strategies have been shown to be effective in the prevention of relapse and recurrence.[8] Nonetheless, drug treatments are by no means ideal. In particular, they appear to be largely symptom-suppressive rather than curative. That is, although they are effective in the treatment of the acute episode and preventive so long as they are continued or maintained, there is no evidence that they reduce risk once their use is discontinued. This is best illustrated by the clear advantage evidenced by continuation medication over medication withdrawal. In a review of seven studies involving nearly 500 patients, Prien and Kupfer found that providing continuation medication for recently remitted patients

reduced risk of relapse relative to withdrawal onto a pill-placebo by nearly 60% (continuation medication was associated with a relapse rate of 20% versus a rate of 48% for the placebo controls; .48-.20/.48 = 58%).[8] Even once the episode is resolved, many depressed patients remain at elevated risk for recurrence.[2] For example, Frank and colleagues found that 80% of all patients with recurrent depression experienced the onset of a new episode within three years of withdrawal from medication, despite having shown a good response to an extended period of prior treatment.[9] They concluded that recurrent depression is a "...chronic disabling condition…" (p. 1093) and implied that such patients may need to be maintained on medication indefinitely.

3. CT as a preventive intervention. There are indications that CT may reduce risk following treatment termination (see Hollon, Shelton, & Loosen, 1991, in Appendix 1).[10] CT is a psychosocial intervention designed to alter the symptomatic expression of depression and reduce risk for subsequent episodes by correcting the negative beliefs and maladaptive information processing presumed to underlie the disorder.[11] Several studies, including our own, have suggested a prophylactic effect following treatment termination for prior CT relative to prior medications.[12-15] Across these trials, prior CT was associated with an average reduction in risk of nearly 60% relative to medication withdrawal (actual relapse rates averaged 26% for prior CT vs 64% for prior medications; .64-.26/.64 = 59%).[16] The magnitude of this effect is virtually identical to that already cited for continuation medication.[8] In the one trial in which they were compared, prior CT performed at least as well as continuation medication with respect to the reduction of subsequent risk (see Evans et al., 1992, in Appendix 1).[15] There is, at this time, no evidence of such a preventive capacity for any other psychosocial intervention following treatment termination. Interpersonal psychotherapy (IPT) does appear to reduce risk so long as it is maintained,[9] but not once its use is terminated.[17] Further, the magnitude of IPT's maintenance effect appears to be considerably smaller than that observed for maintenance medication.[4] Thus, there is reason to think that CT might have a "true" prophylactic effect (i.e., one that extends beyond the termination of treatment) and that this effect may be unique among the existing psychosocial interventions. Moreover, the magnitude of this effect appears to compare favorably to that observed for continuation medications, the current standard of treatment.[8]

4. Rationale for combined and continuation treatment. We have elected to adopt two related strategies to deal with the issues of differential retention and the failure to distinguish between relapse and recurrence. First, we have chosen to implement CT in the context of a combined treatment condition. Since the bulk of the speculation regarding the operation of a "differential sieve" concerns factors related to the presence or absence of medications, implementing CT as a combined treatment means that we can provide all patients in the trial with a common pharmacologic regimen. Since the literature suggests that CT's apparent preventive effect is robust with respect to whether it is provided alone or in combination with medications,[10] such a strategy should provide a fully informative test of the prevention hypothesis while simultaneously reducing the risk of artifact related to differential retention. Second, we hope to differentiate relapse from recurrence by continuing all patients on study medications until they are past the period of risk for relapse. In this fashion, we hope to provide a relatively pure test of CT's capacity to prevent the onset of new episodes, a test largely protected from the threat of differential retention and largely free from the tendency to mistake relapse for recurrence.

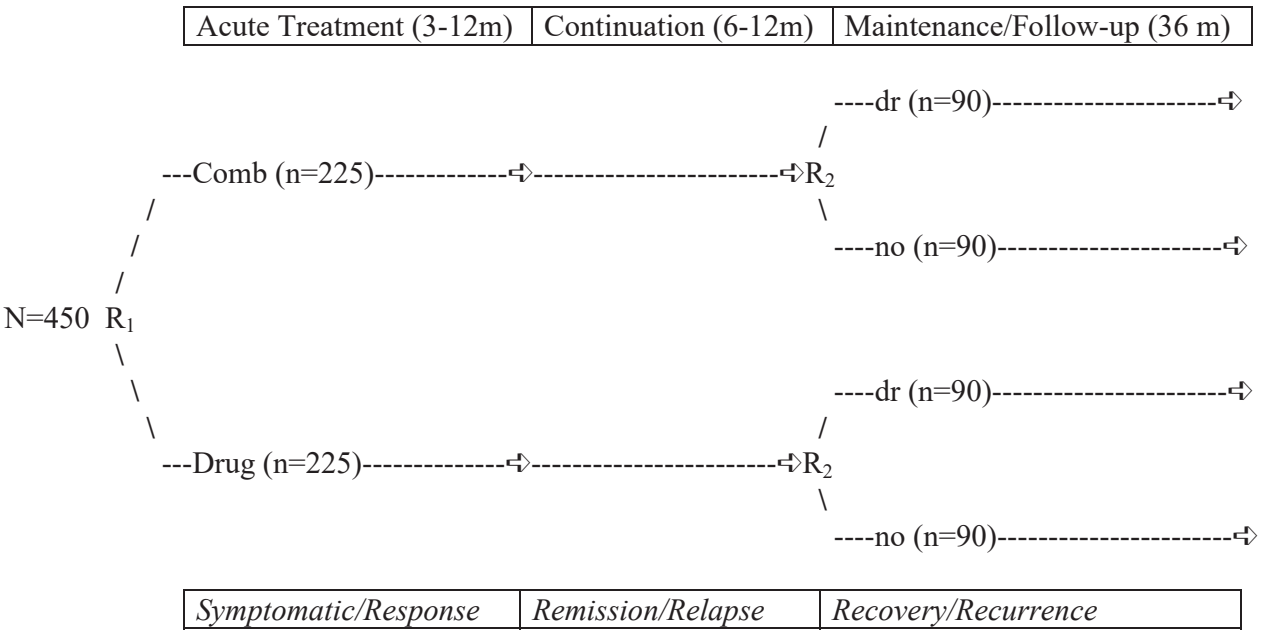
5. Does adding CT enhance acute response to medications? It is possible that combined treatment will produce better acute response than ADM alone (see Hollon et al., 1991, in Appendix 1).[10] The literature has been inconclusive in this regard. In two studies, a significant advantage was obtained for the combination relative to ADM alone,[23,24] but differences were not significant in several other studies,[25-27] including our own (see Hollon et al., 1992, in Appendix 1).[28] Nonetheless, in virtually every existing trial, combined treatment has been associated with a modest, even if non-significant, advantage over ADM alone. Effect sizes on the order of .25 have been typical.[10] What this suggests is that adding CT may enhance the effects of ADM, but that sample sizes typically have been too small to document this effect. As noted by Kazdin and Bass,[29] the comparative treatment literature is replete with studies lacking adequate power to detect clinically meaningful effects. This is particularly likely to be the case when a psychotherapeutic

component is added to a drug treatment already known to be clinically effective.[30] Although our interest in acute response is secondary to our interest in the prevention of recurrence, we will be able to examine whether adding CT to ADM enhances acute response in a sample large enough to detect a small but clinically meaningful effect.

B. Experimental Design and Methods

1. Overview. We plan to examine whether combining ADM and CT improves on ADM alone with respect to both initial response and the prevention of subsequent recurrence. As depicted in Figure 1, we plan to execute a two-cell comparison of ADM alone versus combined treatment during acute and continuation phases, each of which will last up to twelve months. This initial design will then lead into a subsequent 36-month comparison that crosses prior exposure to CT with three different levels of maintenance treatment (active medication vs pill-placebo vs no-pill conditions). Our primary question is whether prior exposure to CT reduces risk for subsequent episodes of depression; that is, whether it prevents recurrence. Our secondary question is whether combined treatment is more effective than ADM alone with respect to initial response.

Figure 1. Overview of Study Design



(a) Acute treatment phase. We plan to randomly assign a total of 450 depressed non-bipolar outpatients (150 at each of three sites) to either ADM alone or combined ADM plus CT (n=225 per condition). All patients will be seen at regular intervals by a study psychiatrist, whereas those patients assigned to the combined treatment will also see a cognitive therapist. Since our goal is to maximize response while minimizing attrition, we plan to provide an approach to drug treatment that is simultaneously both flexible and aggressive. That is, all ADM's will be titrated to the maximum tolerated dosage before the patient is switched to an alternative medication. Patients will have up to 18 months to meet criterion for remission.

(b) Continuation phase. Patients who meet the criterion for remission (one month of minimal symptoms) will enter the continuation phase. Medication treatment will continue as before in all respects. CT will be continued in the combined condition as needed. Whereas many remitted patients will need little more than occasional booster sessions, prior experience suggests that those patients whose depressions are superimposed on a history of chronic dysthymia or long-standing personality disorder may

need continued CT to produce lasting change.[34] Patients who exhibit a return of symptoms (relapse) during the continuation phase can have their medications increased or changed (in accordance with the sequence previously described). If in the combined condition, patients who have relapsed can have, in addition, more frequent CT sessions reinstated. Patients will have up to 12 months to meet criteria for recovery.

(c) Maintenance/follow-up phase. Patients who meet criteria for recovery (going an additional six months, without relapse, from the point of remission) will be withdrawn from any ongoing CT, and randomly assigned to one of two conditions: (1) maintenance medication, or (2) withdrawal from all pills. All patients will then be monitored over a subsequent three-year follow-up period for the onset of new episodes (recurrences) or for any unscheduled return to treatment. Evaluators will be kept blind as to treatment condition. By superimposing this second randomization upon the first, the result is a four-cell design, one that crosses prior CT (present versus absent) with two levels of maintenance medication. This allows us to assess the effects of prior CT for patients both on and off active medications. Inclusion of the maintenance medication condition allows us to ascertain just how well prior CT prevents recurrence compared to ongoing ADM, which is the current standard of treatment in that regard. Inclusion of the no pill condition allows us to estimate the actual magnitude of any enduring effects associated with prior CT.

2. Sample. The patients will be 450 depressed outpatients who meet the following inclusion criteria: (a) diagnosis of major depressive disorder (MDD), according to DSM-IV criteria;[54] (b) minimum score of 16 or above on the first 17 items of the Hamilton Depression Rating Scale (HRSD),[56] (c) age 18 or older; and (d) able and willing to give informed consent. Patients will be excluded if they meet any of the following criteria: (e) history of bipolar affective disorder; (f) history of psychosis (including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, or psychotic organic brain syndrome); (g) current non-psychotic Axis I disorder if it constitutes the predominant aspect of the clinical presentation and if it requires treatment other than that offered in the project (including anxiety disorders, somatoform disorders, dissociative disorders, or eating disorders, etc.); (h) history of substance dependence in the past six months; (i) antisocial, borderline, or schizotypal personality disorder; (j) subnormal intellectual potential (IQ below 80); (k) evidence of any medical disorder or condition (including pregnancy or risk of pregnancy) that could cause depression or preclude the use of study treatments; (l) current treatment with catecholaminergic antihypertensive medication, including reserpine, beta-blockers, clonidine, alphamethyldopa, etc. (diuretics, ACE inhibitors and calcium channel inhibitors will be allowed); (m) clear indication of secondary gain (e.g., court ordered treatment or compensation issues); or (n) current suicide risk sufficient to preclude treatment on an outpatient basis (any patient scoring 3 or above on the suicide item on the HRSD must be cleared for study participation by the medical director). There will be no other restrictions on prior treatment. Thus, the sample will include patients who have been "treatment resistant."

3. Procedures.

(a) Recruitment and pre-screening. All subjects will be drawn from individuals requesting treatment at one of the participating clinics. Persons contacting the clinics will be informed about the project by clinic personnel if it appears that it might be appropriate for them. Potential participants who express an interest will be contacted by the project coordinator and provided with details regarding study participation. The project coordinator will then conduct a brief pre-screening interview (including a review of diagnostic suitability and administration of the HRSD). Potential participants currently on psychoactive medications will be asked to consult with their prescribing physician regarding the advisability of medication withdrawal. Only patients who can be withdrawn safely prior to screening will be scheduled for an evaluation, and then only following a minimum seven-day "washout" period (fourteen days for the MAOI's and fluoxetine). Project psychiatrists will monitor patient status during this withdrawal period. Patients who are in psychotherapy at the time of screening must agree to discontinue before they are assigned to treatment. Recovered patients will be asked not to pursue additional treatment for depression prior to recurrence during the maintenance/follow-up phase. These are similar to the procedures we have used in our current and prior treatment projects (see "Progress Report/Preliminary Studies").

(b) Screening. Potential participants who meet all pre-screening criteria will be scheduled for an intake evaluation within seven days. On the day of the intake evaluation, prospective subjects will first meet with the project coordinator to review details of study participation and to secure informed consent. The intake evaluation itself will consist of two clinical interviews (one with a PI or Co-PI) and a battery of self-report instruments. Prospective patients will also be given a physical exam and screened on a standard medical battery, if indicated. This battery may include blood chemistry (including glucose, SGOT, SGPT, alkaline phosphatase, creatinine, total protein, albumin, BUN, total bilirubin, calcium, gamma glutamyl transferase, uric acid, TSH, and cholesterol), hematology (including CBC and differential), urinalysis (including pregnancy test for females and drug screen for all patients), and ECG. The purpose of this battery is to rule out any medical condition that would preclude study participation.

(c) Randomization. Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomly assigned to treatment condition, blocking on gender, severity, marital status, number of prior episodes, and presence or absence of underlying personality disorder.

4. Assessments. Table 1 presents an overview of the assessment schedule. We plan to conduct complete evaluations at intake, at the beginning of continuation (remission), at the beginning of maintenance/follow-up (recovery), and yearly during follow-up. In addition, we plan to conduct brief symptom-focused reevaluations after 2, 4, 8, 12, 16, and 20 weeks of acute treatment, and at 8-week intervals thereafter during acute treatment. During the continuation phase (after patients have met criteria for remission), we plan to conduct symptom-focused reevaluations on a bi-monthly basis, supplemented by more extensive retrospective assessments of prior symptoms. During the maintenance/follow-up phase (after patients have met criteria for recovery and following the second randomization), we plan to conduct brief symptom-focused reevaluations monthly for the first three months, and every three months thereafter (supplemented by monthly phone calls and mailers).

(a) Diagnostic. The Structured Clinical Interview for DSM-IV Axis I Disorders--Patient Version (SCID-I/P) will serve as the primary instrument for diagnostic ascertainment.[59] The SCID-I/P is a semi-structured psychiatric interview designed to yield judgments with respect to all five axes in the DSM-IV.[54] It also incorporates criteria for assessing specific subtypes of depression, including endogenous and atypical depression. All SCID-I/P interviews will be videotaped and a random subset rated by evaluators at the other sites to assess diagnostic reliability and cross-center generality. In addition, all prospective patients will be seen by a senior clinician (PI or Co-PI) prior to randomization.

Table 1. Schedule of Assessments

Scale	D/R	Intake 0	Acute (weeks) 2 4 6 8 12-->52	Cont (months) 2 4 6-->12	Maintenance/Follow-up (Months) 3 6 9 12 15 18 21 24 27 30 33 36
SCID-I/P	a1	x			
LIFE	a2		x x x x	x x x x x	x x x x x x x x x x x x
FH-DSM	b1	x			
Med Bat	b1	x			
Shipley	b1	x	x	x	x
BDI	c2	x	xxxx x x x x x x	xxxxxxxxxxxx	xxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
HRSD	c2	x	xxxx x x x x x x	xxxxxxxxxxxx	xxx x x x x x x x x x x x
BAI	c2	x	x x x x x	x x x x x x	xxx x x x x x x x x x x x
HRSA	c2	x	x x x x x	x x x x x x	xxx x x x x x x x x x x x
SF-36	d2	x	x x x x x	x x x x x x	xxx x x x x x x x x x x x
GAF	d2	x	xxxx x x x x x x	xxxxxxxxxxxx	xxx x x x x x x x x x x x
SAS	d2	x	x x x x	x	x
SCID-II	e1	x	x	x	x
NEO	e1	x	x	x	x
CSPRS	f3		s----------→	s----------→	s----------→
CTS	f3		s----------→	s----------→	
CMS	f3		s----------→	s----------→	s----------→
WAI-P	f4		s----------→	s----------→	s----------→
WAI-T	f4		s----------→	s----------→	s----------→
WAI-O	f4		s----------→	s----------→	s----------→
ASQ	g5	x	x x x x	x	x
HS	g5	x	x x x x x	x	x
DAS	g5	x	x x x x	x	x
WOR	g5	x	x x x x	x	x
PERI	h1	x	x x x x	x x x x x x	x x x x x x x x x x x x

Key
Domain (D): a = diagnostic, b = descriptive, c = symptomatic, d = quality of life, e = personality, f = treatment process, g = cognitive, h = life event;
Role (R): 1 = prediction, 2 = outcome, 3 = adherence/competence, 4 = process, 5 = mediation;
Administration (A): x = all subjects, s = selected sessions.

(b) Descriptive. We plan to use the Family History-Research Diagnostic Criteria (FH-RDC), modified to yield DSM-IV diagnoses, as a means of ascertaining family histories. The FH-DSM will be obtained by the project evaluator at the intake interview, using the family history method.[61] The medical battery has already been described. We also plan to use the Shipley-Hartford as a quick screen for intellectual capacity.[62]

(c) Symptomatic. We plan to use two measures of depressive symptoms, the Beck Depression Inventory (BDI),[55] the most widely used self-report measure, and the HRSD,[56] the most widely used clinician-rated measure. The HRSD will be administered according to the interview guide developed by Williams, modified to retain the original order of the items.[63] In addition, we plan to use two measures of anxiety symptoms, the Beck Anxiety Inventory (BAI),[64] a self-report measure designed to minimize overlap with the construct of depression, and the Hamilton Rating Scale for Anxiety (HRSA),[65] a widely used clinician-rating scale.

(d) Quality of life. We plan to assess patients' overall adjustment/quality of life and with one interview-based scale, and two self-report measures. Overall adjustment/impairment will be assessed using the clinician-rated Global Assessment of Functioning scale (GAF),[66] which was found to predict differential response to CT versus ADM in the TDCRP.[57] The SF-36 is widely-used in medical research to

assess general satisfaction with the quality of life.[67] Finally, the self-report Social Adjustment Scale (SAS)[68] will be used to assess broad areas of social and occupational funtioning.

(d) Personality. A number of studies have documented the high co-morbidity of personality disorders and depression. Two measures of personality disorder and/or personality dimensions will be used, the SCID-II (revised for DSM-IV)[69] and the NEO Five Factor Inventory (NEO).[70]

(e) Treatment process. We plan to use several measures of treatment process to provide checks on the adequacy of treatment implementation, and to allow us to discern the determinants of change.

(f) Cognitive. Several measures of cognitive processes will be included (see Table 1).

(g) Life events. We plan to use a modified version of the Psychiatric Epidemiology Research Interview (PERI) Life Events scale, a self-report measure of life events.[84] We plan to ask subjects to complete the PERI at intake, monthly during acute treatment, bimonthly during continuation, and every three months thereafter.

5. Treatment components. Both active treatment conditions are standard interventions that we have used in previous studies. All patients will be treated with medications, as described below. Half of those patients will also receive cognitive therapy during acute and (as needed) continuation treatment as the other component of combined treatment. The specific treatment components are:

(a) Pharmacotherapy. In an effort to maximize response while minimizing attrition, we plan to use up to four different medications (along with possible augmentation) in drug treatment. All patients will start on venlafaxine, a serotonin reuptake inhibitor that also has effects on norepinepherine at higher doses (it is thus known as an NSRI).[50,51] Venlafaxine will be started on 37.5 mg per day and incremented in 37.5 mg steps at least every other week (to a maximum of 225 mg) until the patient either shows a full response or experiences dose limiting side effects. Side effects will be handled by slowing the titration schedule or temporarily reducing the dosage before reinitiating dose escalation. Patients who show a partial response to venlafaxine can be augmented with lithium (in the manner described below), prior to being switched to the next medication in the sequence. Patients who fail to respond to venlafaxine will be switched to nortriptyline, a tricyclic antidepressant (TCA) that has its primary effects on the noradrenergic system. Patients switched to nortriptyline will be started on 25-50 mg per day and incremented in 25-50 mg steps at least every other week (to achieve a plasma level between 80-150 ng/ml) until they either show a full response or experience dose limiting side effects. As for venlafaxine, side effects will be handled by slowing the titration schedule or temporarily reducing the dosage before reinitiating dose escalation. Patients who do not show a full response to nortriptyline will be augmented with lithium, in the manner described below. The TCA's were the former standard of treatment before the introduction of the SSRI's. Some patients will respond to those medications who do not respond to either an SSRI or a NSRI.[52] Finally, those patients who fail to respond to nortriptyline will be switched to tranylcypromine, a monoamine oxidase inhibitor (MAOI). Tranylcypromine will be started at 20 mg per day and advanced as required and tolerated to a maximum of 60 mg per day. As with the previous medications, patients who fail to respond to tranylcypromine will be augmented with lithium (in the manner described below). SSRIs will be an option at each step, depending upon the clinical judgment of the study doctor, in consultation with the other study doctors. By adopting these strategies, we hope to maximize the likelihood of response by exposing each patient to up to four different kinds of medications (each of the major classes of ADM), plus augmentation. At the same time, we hope to minimize attrition by choosing the most readily tolerated class of medication (as well as the best tolerated medication within each class) at each step along the way.

Patients who fail to show a full response to venlafaxine (or any of the subsequent medications) can be augmented with lithium. Although the number of controlled studies are few, there are indications that lithium can be an effective augmentation agent for a variety of antidepressant medications.[88,89] It makes little sense to augment a patient who shows little or no response to a given medication, but augmentation can be helpful for patients who show at least a partial response.[52] Patients who are augmented with lituhium will be started on a dosage of 600 mg per day, and will have their serum lithium level assessed

after 5 days and again at 3 weeks. Dosage will be adjusted within the range of 600-1500 mg so as to achieve a lithium serum level between 0.6 mmol/L and 1.2 mmol/L. Blood will be drawn every 3 months thereafter to check on Li serum levels. Additional lithium levels will be obtained as needed by the treating psychiatrist.

By adhering to this schedule, we should be able to ensure that each patient can be exposed to an array of medications representing the major classes of ADM (NSRI, TCA, MAOI, and SSRI), plus augmentation, in an effort to maximize response and minimize attrition. Patients who cannot tolerate or respond to a given medication will sometimes tolerate and respond to another. Our best estimate is that at least half of the patients started on venlafaxine will respond to that medication and that as many as half of the patients switched (or augmented) will respond at each successive step along the way. Prior comparisons of ADM and psychotherapy have been criticized for providing inadequate and unrepresentative drug treatment by virtue of sticking to a single medication and not permitting augmentation.[90] That is clearly not what is done in high quality clinical practice. By adopting a sequential medication strategy (plus augmentation), we think that we can do a better job of representing actual clinical practice, while retaining necessary rigor, than is done in most controlled clinical trials.

Decisions regarding dose escalation, the handling of side effects, when to augment with lithium, and when to switch medications will be discussed each week in ongoing supervision sessions at the respective sites. The progress of each patient in the trial is reviewed during these meetings and clinical choice points discussed to ensure that protocol is implemented in a comparable fashion across therapists. These decision strategies are reviewed in biweekly conference calls and at least annually in joint meetings to ensure that protocol is implemented in a comparable fashion across sites. This provides the flexibility to meet the clinical needs of the patient, yet retains the rigor required of a controlled empirical trial.

Clinical management sessions will be conducted in a manner consistent with the manual developed by Fawcett and colleagues for the TDCRP.[91] Formal re-educative and re-constructive psychotherapeutic procedures are prohibited, but supportive procedures and some limited advice-giving are encouraged, along with general regimen management. Sessions will typically last about 20 minutes, although initial sessions may take up to an hour. Side effects will be monitored at each visit and handled by slowing the titration schedule or reducing the medication dosage temporarily. The treating physician will conduct a pill-count at each session to monitor compliance. Patients who have not taken at least 75% of the prescribed medication dose in any two-week period will be considered to be non-compliant. Chloral hydrate and zolpidem will be allowed to deal with sleep difficulties. Drugs without CNS effects will not be specifically precluded, except as noted in the inclusion/exclusion criteria. Any deviation from the PT protocol will require the consent of both Dr. Fawcett and the specific site supervisor.

Patients who have met criteria for remission will be continued on study medications for at least an additional six months. Session frequency can be reduced during the continuation phase to monthly contacts. Treating psychiatrists will be free to adjust medication levels as necessary, but it is expected that doses will be continued at full acute treatment levels. Patients who meet criteria for recovery (an additional six months without relapse) will be withdrawn from CT (if in combined treatment) and randomly assigned to one of two conditions: (1) maintenance medications, or (2) withdrawal from all pills. Patients will continue to meet with their treating psychiatrist at least monthly for the first three months of maintenance/follow-up and at least every three months thereafter, irrespective of whether they are maintained on medication.

(b) Cognitive Therapy. CT will be conducted according to the manuals published by Beck and colleagues.[11,35] The intervention consists of a series of structured, partially didactic sessions targeted initially at promoting behavioral activation and disconfirming specific negative expectations. As treatment progresses, the emphasis shifts to the identification and evaluation of more abstract underlying beliefs and attitudes. Given our interest in prevention, we emphasize a skills-training approach designed to ensure that patients can function as their own therapists by the end of treatment. Moreover, we devote considerable

time in later sessions to anticipating and practicing the management of potentially distressing life events and the return of symptoms.

6. Definitions of clinical course. Definitions of remission/recovery and relapse/recurrence are critical to the design, not only because they serve as dependent measures, but also because they provide the basis on which decisions will be made regarding subsequent treatment. We plan to follow the guidelines laid out by the MacArthur Task Force in distinguishing between remission versus recovery, and relapse versus recurrence.[19]

7. Analytic strategy. We will first assess the adequacy of randomization by comparing the treatment conditions on the various demographic, symptomatic, history of illness, and other indices collected at intake. Treatment condition and site will serve as the independent variables. In the event that site differences or interactions are observed, we will estimate treatment effects separately within site and pool across settings, so as to minimize the risk of confounding site with treatment effects.[94] This same procedure will be used to handle site differences in all subsequent analyses. Analyses of variance (ANOVA's) will be used for the continuous variables and non-parametric analyses (X^2's) will be used for the categorical variables. Any variable on which the treatment conditions differ (adopting a relaxed alpha level of .10) will be entered into a univariate linear regression[95] or proportional hazards linear regression[96] to determine its relation, respectively, to response or recurrence. Any variable which both differentiates between the treatment conditions and predicts subsequent response or recurrence (after controlling for the effects of treatment and again adopting a relaxed alpha level of .10) will be considered a potential confound and entered as a covariate in all relevant subsequent analyses. Specific hypotheses follow each section.

(a) Acute response. We plan to conduct three types of analyses with respect to acute response. First, we plan to conduct standard analyses of covariance on data collected over the first three months, when all patients remain in active treatment. In this regard, we plan to conduct separate multivariate analyses of covariance (MANCOVA's) on the constructs of depression (BDI and HRSD), anxiety (BAI and HRSA), and general adjustment/life satisfaction (SF-36 and GAS), followed by separate univariate analyses, when appropriate. Treatment condition (ADM alone versus combined treatment) and site will again serve as between-subjects factors, with pretreatment scores on the respective constructs or single variables serving as the covariates (along with any confounds identified). These analyses will be conducted as endpoint analyses (carrying forward the last available assessment on any noncompleter) on the "intent to treat" sample and as standard analyses on the "completers" sample.[97] Second, we plan to supplement these analyses by applying random regression models (RRM's) to the longitudinal measures of treatment response.[98] RRM's allow for missing observations and subjects measured at different points in time, common features in longitudinal data sets, as well as estimation of random person-specific effects. Recent reanalyses of the TDCRP data have shown that RRM's were more sensitive to treatment effects initially masked by attrition than were conventional repeated measures analyses of variance.[46,99] Comparisons will be made between the two initial treatment conditions (ADM alone versus combined) through the first three months (when all patients remain in acute treatment and differences in mean scores should be most apparent) and beyond, through the duration of acute treatment. Finally, we will also conduct survival analyses on the variable "time to remission," with treatment condition and site as the independent variables and time-to-remission as the dependent variable.[100] The Kaplan-Meier product limit method will be used to generate survival curves for each treatment condition.[101] Although survival curves treat time as the dependent variable, statistics based on proportional data are typically used to test for differences between the conditions. Specifically, we plan to use the Mantel-Cox test (also known as the logrank test) to test for group differences.[102]

Based on our previous work (and that of others) we expect differences of the following magnitude. With respect to each of the symptom measures (BDI and HRSD), we estimate that we will find differences favoring combined treatment of at least 2 points, with a standard deviation of 6, through the first three months of treatment. This is a small-to-moderate effect, one that is clinically meaningful and consistent with the previous literature, but one that has often fallen short of statistical significance in early studies with

smaller sample sizes. With a sample of 450 (180 per condition), power to detect such an effect using a two-tailed test with alpha = .05 should be in excess of .90 in the "intent to treat" sample and in excess of .80 among patients who complete treatment (even allowing for a 20% attrition rate).[103] Similarly, RRM's through month three and beyond should have more than adequate power to detect any reasonable sized effect. Nonparametric analyses (X^2's) on response/non-response and Jacobson's index of clinically meaningful change will also be applied to the month three data to ensure that trivial clinical differences are not over-interpreted merely because they are statistically significant.[104] Time-to-remission will serve as the primary dependent variable for the survival analyses. Given our previous studies, we can estimate that approximately 65% of the patients assigned to combined treatment will remit within the first three months, compared to 50% of the patients assigned to ADM alone. This difference in probability of remission within a fixed period of time should reflect a difference in underlying rate of response. We can estimate that patients in combined treatment should, on average, meet criteria for remission about 15% sooner than patients treated with ADM alone. Again, given a sample of 450 (225 per condition), power to detect such an effect using a two-tailed test with alpha = .05 should be in excess of .90.[105] Based on past experience, we expect virtually all of the patients to remit by the end of month twelve, but we do expect differences in the rate of remission, with patients assigned to combined treatm**ent showing a small-to-moderate sized advantage over patients assigned to ADM alone.

Hypothesis 1: Patients assigned to combined treatment will show greater response within a fixed period and meet criteria for remission at a more rapid rate than patients assigned to ADM alone.

(b) Differential relapse. We do not have strong predictions with respect to differential relapse during the continuation phase. Although we expect patients in combined treatment to be at reduced risk, we suspect that continuing all patients on active medications will suppress any strong indications of such an effect. Nonetheless, we will conduct survival analyses on "time-to-relapse," treating initial remission as the point at which patients enter the period of risk. As with time-to-remission, the Kaplan-Meier product limit method will be used to generate survival curves for each treatment condition,[101] and the Mantel-Cox test will be used to test for group differences.[102] Based on our prior experience, we expect rates of relapse among medicated patients to be small (about 10-20%) and differences between the treatment conditions to be minimal.

Hypothesis 2: Although any differences observed will likely favor combined treatment, we do not expect significant differences in relapse between the treatments during the continuation phase.

c) Differential recurrence. We do have strong predictions concerning differential recurrence. At the point of entry into the maintenance/follow-up phase, all recovered patients will be randomized a second time into one of two treatment conditions: (1) maintenance medication, and (2) withdrawal from all pills. This second randomization will have been superimposed upon the first, resulting in a four-cell design, such that half of the patients in each of the above conditions will have been treated previously with combined treatment, whereas the other half will have been treated with ADM alone. Extrapolating from prior experience in the Minnesota project (see Evans et al., 1992, in Appendix I) and the findings from other similar projects,[12-15] including the recent study by Fava and colleagues dealing directly with recurrence,[22] we expect prior CT to reduce risk for recurrence by at least 50% among patients withdrawn from medications, an effect comparable in size to the protection afforded by maintaining the patient on active medications. Thus, we expect recurrence rates in excess of 50% for patients initially treated with ADM alone who are withdrawn from medications following recovery, versus rates of recurrence of 20% or less for patients who either had prior exposure to CT (combined treatment) or who are maintained on active medication. Based on these estimates and an initial sample of 450 patients (113 per condition, at least 90 of whom should complete all treatment procedures and meet criteria for recovery), we should have power in excess of .80 for a two-tailed test.[105] This was the critical power calculation that led us to set our sample size at N=450.

Hypothesis 3: Patients previously assigned to combined treatment will fare better than patients treated with ADM alone following medication withdrawal and will be no more likely to experience the onset of new episodes than patients maintained on active medications.

(d) Prediction of response and recurrence. Proportional hazards linear regressions will be used to evaluate predictive status with respect to time to remission and subsequent time to recurrence (similar analyses will be conducted with respect to relapse, but given that all patients will be kept on continuation medications, we make no strong predictions in that regard).[96] With respect to time-to-remission (response to acute treatment), each potential predictor, treatment condition (combined treatment versus ADM alone), and the predictor-by-treatment interaction will be entered as independent variables in the respective models. A significant main effect for a predictor indicates nonspecific prognostic status, whereas a significant treatment-by-predictor interaction indicates that the variable is a differential prescriptor (i.e., an index that can be used to determine whether a specific type of patient benefits from the addition of CT to medications). The same basic strategy will be used to assess time-to-recurrence, with the number of treatment conditions increased from two to six in a two (combined versus ADM alone) by two (maintenance medications versus no pill) design and the period of risk starting at the point of recovery. As in the prediction of response, a significant main effect for the predictor will indicate general prognostic status, whereas a significant predictor-by-treatment interaction will indicate potential prescriptive status. As before, interactions will also be explored and significant predictors will be combined in a stepwise multivariate proportional hazards linear regression to eliminate redundant indices.

Hypothesis 4: Severity, chronicity, and presence of an underlying personality disorder should each predict response to treatment (time-to-remission) and differential response to combined treatment. These same indices (substituting number of prior episodes for initial severity) should predict higher and differential rates of recurrence. That is, patients with a prior history of frequent episodes or chronic depression, or who have an underlying personality disorder, should be those patients who most benefit from combined treatment (adding CT to medications).

E. Human Subjects

1. Patients. Patients will be either self-referred or referred by other agencies or professionals to the Depression Research Unit. We anticipate that approximately two-thirds of the sample will be female, and that approximately 15% will be minority. These rates are consistent with the rates for MDD found in the United States. Thus, our findings should generalize to the population at large, at least in respect to sex and race/ethnicity.

2. Potential risks. The potential risks of participation in the project include those associated with the assessment procedures and those associated with the treatments. With regard to the assessment procedures, the venipuncture used in the biological assays carries the risk of bleeding, bruising, and infection at the site. Patients receiving medications may experience a number of different side effects. These include dry mouth, blurred vision, constipation, nausea, vomiting, fatigue, nervousness, anxiety, insomnia, restless sleep, daytime drowsiness, headaches, rash, tremor or anxiety, increased sweating, diarrhea, urinary retention, dizziness (including orthostasis), hypomania or mania, appetite change with weight gain or loss, myoclonic jerks, paresthesias, and sexual side effects such as loss of interest, inability to experience orgasm, and impotence. Venlafaxine infrequently may cause mild and transient increases in blood pressure. In very rare instances, nortryptyline can cause more serious events such as severe allergic reactions (e.g., angioneurotic edema), atrioventricular conduction delay (and related cardiac events), falls, seizures, or syncope. Confusion, coma, or death may happen with overdoses. Tranylcypromine is a MAOI. It may cause adverse interactions with certain foods (i.e., those containing large amounts of the amino acid tyramine) or drugs. Drugs that must be avoided include (but are not limited to) sypathomimetics, other antidepressants, meperidine, buspirone, or dextromethorphan. Certain medicinal herbs such as Ma Huang (Ephedra), valerian root, licorice root, and St. John's Wort should also be avoided. These interactions may induce marked hypertension, confusion, psychosis, agitation, or other negative effects. Possible allergic reactions to the medications include skin rash and other cutaneous reactions, inflammatory liver reactions, and other more serious responses including angioneurotic edema. These are usually mild and self-limiting. ADM's pose unknown risks to pregnant women and their fetuses. Patients receiving lithium carbonate may experience side effects such as nausea, vomiting, diarrhea, tremor, polydipsia, polyuria, increased thirst, weight gain, fatigue, slurred speech, and ataxia. Allergic reactions to lithium include skin rash and other cutaneous reactions. These are usually mild and self-limiting. Further, lithium poses known cardiac risks including rare heart rhythm disturbances including sick sinus syndrome and even sudden death. Kidney toxicity including nephrotic syndrome, syndrome of inappropriate ADH, nephrogenic diabetes insipidus, and other effects may occur. Hypothyroidism with or without diffuse goiter may also occur. There are reported risks in pregnancy. This especially includes Ebstein's Anomaly. Lithium can also be a problem during lactation, since the ion is secreted in breast milk and can result in toxicity to the infant. If serum concentrations rise above 2 mmol/L, more serious toxic reactions may occur. These can include severe tremor, nausea, vomiting, muscular rigidity, increased deep tendon reflexes, dysarthria, confusion, coma, and death. Lithium augmentation has also been reported to induce hypomania or worsening depression in some patients. Patients withdrawn from active medications during the maintenance phase may be placed at elevated risk for recurrence. Finally, all patients will be placed at risk by virtue of being asked to provide sensitive and personal information.

3. Safeguards. The following steps will be taken to reduce or ameliorate the risks described in the previous section. Venipuncture will be conducted only by highly trained, experienced medical personnel. Emergency and long-term care are available, if needed, through the Medical Centers at the respective sites. Patients will receive a physical exam, ECG, and laboratory evaluation at intake, prior to drug treatment, to evaluate for any medical condition that would preclude the use of ADM. Risks inherent in the use of sertraline or venlafaxine are intrinsic to the use of any such SRI. These medications were selected because the SSRI's and related medications tend to be associated with fewer troublesome side effects than other types of antidepressants. It should be noted that the SSRI's have become the new standard of treatment for depression, and that augmentation with lithium has become a well-established treatment for episodes of

depression that are resistant to a single antidepressant medication. Risks inherent in the use of nortriptyline are intrinsic to the use of any such TCA. Nortriptyline was selected because it has a relatively low side effect profile and because drug levels can be monitored with periodic plasma levels. Risks inherent in the use of lithium can generally be avoided by careful dose titration, along with serum and clinical monitoring. Patients who will be treated with tranylcypromine will be fully informed about all risks, side effects, and, especially, interactions with drugs or foods. Each of these patients will be given a complete list of foods and drugs (including herbs) to avoid. In addition, we will ask them to report and clear all new medications before initiation. All patients will be carefully monitored by their treating psychiatrist, with whom they will meet at least biweekly during acute treatment, at least monthly during continuation, and at least every three months during maintenance. All patients will be provided with emergency contact numbers. All women of childbearing potential will be informed of the potential complications of becoming pregnant while on medications and all will be HCG tested at intake and again before lithium augmentation to ensure that they are not pregnant. All women of childbearing potential must be practicing adequate birth control, and they will be instructed not to become pregnant during medication treatment. Lactating women will not be included. With regard to the risks associated with being withdrawn from medications following recovery, all such patients will be carefully monitored and those who exhibit a recurrence will be offered a subsequent course of drug treatment for the duration of the follow-up, at project expense. Study personnel, including a project physician, will be available immediately (in person or by phone) if any patient becomes acutely suicidal. The patient care ombudsman will review all such cases to determine the appropriateness of such patients continuing in the study. Inpatient care is available if needed. With regard to the provision of sensitive and personal information, experienced research personnel will conduct all interviews. All information obtained will be stored by code number only. No information will be released to any outside person or agency except at the written request of the patient. All data will be reported only as group aggregates that cannot be associated with any given individual. All data will be stored in secured locations at the respective research clinics. Finally, all patients will be provided with information about alternative sources of treatment, both within the medical center and in the larger treatment community.

4. Risk/benefit ratio. The risks inherent in the assessment procedures are typically of low probability and reversible with appropriate treatment. If anything, the assessment procedures should reduce overall risk, since subjects will be closely monitored even after completing treatment. The risks inherent in the treatment procedures are precisely those associated with what is the current standard for effective treatment of depression in the larger clinical community. The risks associated with medication withdrawal will be kept to the minimum needed to test the questions of interest. Additional treatment will be provided for those who experience a recurrence. The study provides an opportunity to examine the enduring effects of CT and to determine whether it enhances the effects of medications. The project offers a unique opportunity to study the processes and mechanisms involved in any enduring effects that CT may possess, and, as such, may highlight the operation of factors central to the etiology of depression.

Literature Cited

1. Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H., & Kendler, K.S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the Unites States: Results from the National Comorbidity Study. Archives of General Psychiatry, 51, 8-19.
2. Consensus Development Panel (1985). NIMH/NIH consensus development conference statement on mood disorders: Pharmacological prevention of recurrences. American Journal of Psychiatry, 142, 469-476.
3. Zis, A.P. & Goodwin, F.K. (1979). Major affective disorder as a recurrent illness: A critical review. Archivesof General Psychiatry, 36, 835-839.
4. Hollon, S.D., DeRubeis, R.J., & Seligman, M.E.P. (1992). Cognitive therapy and the prevention of depression. Applied and Preventive Psychology, 1, 89-95.
5. Thase, M.E. , & Kupfer, D.J. (1996). Recent developments in the pharmacotherapy of mood disorders. Journal of Consulting and Clinical Psychology, 64, 646-659.
6. Austin, M.P.V, Souza, F.G.M., & Goodwin, G.M. (1991). Lithium augmentation in antidepressant-resistant patients: A quantitative analysis. British Journal of Psychiatry, 159, 510-514.
7. Price, L.H. (1990). Pharmacological strategies in refractory depression. In A. Tasman., S.M. Goldfinger, & C.A. Kaufmann (Eds.), Review of Psychiatry (pp. 116-131). Washington, D.C.: American Psychiatric Press, Inc.
8. Prien, R.F., & Kupfer, D.J. (1986). Continuation drug therapy for major depressive episodes: How long should it be maintained? American Journal of Psychiatry, 143, 18-23.
9. Frank, E., Kupfer, D.J., Perel, J.M., Cornes, C., Jarrett, D.B., Mallinger, A.G., Thase, M.E., McEachran, M.S., & Grochocinski, V.J. (1990). Three-year outcomes for maintenance therapies in recurrent depression. Archives of General Psychiatry, 47, 1093-1099.
10. Hollon, S.D. Shelton, R.C., & Loosen, P.T. (1991). Cognitive therapy and pharmacotherapy for depression. Journal of Consulting and Clinical Psychology, 59, 88-99.
11. Beck, A.T., Rush, A.J., Shaw, B.F., & Emery, G. (1979). Cognitive therapy of depression: A treatment manual. New York: Guilford Press.
12. Blackburn, I.M., Eunson, K.M., & Bishop, S. (1986). A two – year naturalistic follow – up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. Journal of Affective Disorders, 10, 67-75.
13. Kovacs, M., Rush, A.T., Beck, A.T., & Hollon, S.D. (1981). Depressed outpatients treated with cognitive therapy or pharmacotherapy: A one – year follow – up. Archives of General Psychiatry, 38, 33-39.
14. Simons, A.D., Murphy, G.E., Levine, J.L., & Wetzel, R.D. (1986). Cognitive therapy and pharmacotherapy for depression: Sustained improvement over one year. Archives of General Psychiatry, 43, 43-48.
15. Evans, M.D., Hollon, S.D., DeRubeis, R.J., Piasecki, J.M., Garvey, M.J., Grove, W.M., & Tuason, V.B. (1992). Differential relapse following cognitive therapy, pharmacotherapy, and combined cognitive-pharmacotherapy for depression. Archives of General Psychiatry, 49, 802-808.
16. Hollon, S.D. (1990). Cognitive therapy and pharmacotherapy for depression. Psychiatric Annals, 20, 249-258.
17. Weissman, M.M., Klerman, G.L., Prusoff, B.A., Sholomskas, D., & Padian, N. (1981). Depressed outpatients one year after treatment with drugs and/or interpersonal psychotherapy (IPT). Archives of General Psychiatry, 38, 51-55.
19. Frank, E., Prien, R.F., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W., Rush, A.J., & Weissman, M.M. (1991). Conceptualization and rationale for consensus definitions of terms in major depressive disorder: Remission, recovery, relapse, and recurrence. Archives of General Psychiatry, 48, 851-855.
23. Blackburn, I.M., Bishop, S., Glen, A.I.M., Whalley, L.J., & Christie, J.E. (1981). The efficacy of cognitive therapy in depression: A treatment trial using cognitive therapy and pharmacotherapy, each alone and in combination. British Journal of Psychiatry, 139, 181-189.
24. Teasdale, J.D., Fennell, M.J.V., Hibbert, G.A., & Amies, P.L. (1984). Cognitive therapy in major depressive disorder in primary care. British Journal of Psychiatry, 144, 400-406.
25. Beutler, L.E., Scogin, F., Kirkish, P., Schretlen, D., Corbishley, A., Hamblin, D., Meredith, D., Potter, R., Bamford, C.R., & Levenson, A.I. (1987). Group cognitive therapy and alprazolam in the treatment of depression in older adults. Journal of Consulting and Clinical Psychology, 55, 550-556.
26. Covi, L., & Lipman, R.S. (1987). Cognitive-behavioral group psychotherapy combined with imipramine in major depression. Psychopharmacological Bulletin, 23, 173-176.
27. Murphy, G.E., Simons, A.D., Wetzel, R.D., & Lustman, P.J. (1984). Cognitive therapy and pharmacotherapy, singly and together, in the treatment of depression. Archives of General Psychiatry, 41, 33-41.

28. Hollon, S.D., DeRubeis, R.J., Evans, M.D., Wiemer, M.J., Garvey, M.J., Grove, W.M., & Tuason, V.B. (1992). Cognitive therapy, pharmacotherapy and combined cognitive-pharmacotherapy in the treatment of depression. Archives of General Psychiatry, 49, 774-781.
29. Kazdin, A., & Bass, D. (1989). Power to detect differences between alternative treatments in comparative psychotherapy outcome research. Journal of Consulting and Clinical Psychology, 57, 138-147.
30. Hollon, S.D., Shelton, R.C., & Loosen, P.T. (1991). Research considerations in evaluating combined treatment. In B.D. Beitman & G.L. Klerman (Eds.), Integrating pharmacotherapy and psychotherapy (pp. 353-375). Washington, DC: American Psychiatric Press.
46. Elkin, I., Gibbons, R.D., Shea, M.T., Sotsky, S.M., Watkins, J.T., Pilkonis, P.A., & Hedeker, D. (1995). Initial severity and differential treatment outcome in the Nationla Institute of Mental Health Treatment of Depression Collaborative Research Program. Journal of Consulting and Clinical Psychology, 63, 841-847.
50. Richelson, E. (1994). Pharmacology of antidepressants – characteristics of the ideal drug. Mayo Clinic Proceedings, 69, 1069-1081.
51. Nierenberg, A.A., Feighner, J.P., Rudolph, R., Cole, J.O., & Sullivan, J. (1994). Venlafaxine for treatment-resistant unipolar depression. Journal of Clinical Psychopharmacology, 14, 419-423.
52. Nierenberg, A.A., & Amsterdam, J.D. (1990). Treatment-resistant depression: Definition and treatment approaches. Journal of Clinical Psychiatry, 51(6 suppl), 39-47.
53. Fawcett, J., Kravitz, H.M., Zajecka, J.M., & Schaff, M.R. (1991). CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. Journal of Clinical Psychopharmacology, 11, 127-132.
54. American Psychiatric Association (1994). Diagnostic and statistical manual of mental disorders (4th ed.). Washington, D.C.: American Psychiatric Association.
55. Beck, A.T., Ward, C.H., Mendelson, M., Mock, J.E., & Erbaugh, J.K. (1961). An inventory for measuring depression. Archives of General Psychiatry, 4, 561-571.
56. Hamilton, M. (1960). A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry, 23, 56-62.
57. Elkin, I., Shea, M.T., Watkins, J.T., Imber, S.D., Sotsky, S.M., Collins, J.F., Glass, D.R., Pilkonis, P.A., Leer, W.R., Docherty, J.P., Fiester, S.J., & Parloff, M.B. (1989). NIMH Treatment of Depression Collaborative Research Program: I. General Effectiveness of Treatments. Archives of General Psychiatry, 46, 971-982.
58. Efron, B. (1971). Forcing a sequential experiment to be balanced. Biometrika, 58, 403-417.
59. First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B.W. (1994). Structured clinical interview for Axis I DSM-IV Disorders--Patient Edition. Washington, DC: American Psychiatric Press.
60. Keller, M.B., Lavori, P.W., Friedman, B., Nielsen, E., Endicott, J., McDonald-Scott, P., & Andreasen, N.C. (1987). The Longitudinal Interval Follow-up Evaluation. Archives of General Psychiatry, 44, 540-548.
61. Andreasen, N., Endicott, J., Spitzer, R.L., & Winokur, G. (1977). The family history method using diagnostic criteria: Reliability and validity. Archives of General Psychiatry, 34, 1229-1235.
62. Shipley, W.C. (1940). A self-administered scale for measuring intellectual impairment and deterioration. Journal of Psychology, 9, 371-377.
63. Williams, J.B.W. (1988). A structured interview guide for the Hamilton Depression Rating Scale. Archives of General Psychiatry, 45, 742-747.
64. Hamilton, M. (1959). The assessment of anxiety status by rating. British Journal of Medical Psychology, 32, 50-55.
65. Beck, A.T., Epstein, N., Brown, G., & Steer, R.A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. Journal of Consulting and Clinical Psychology, 56, 893-897.
66. Endicott, J., Spitzer, R.L., Fleiss, J.L., & Cohen, J. (1976). The Global Assessment Scale: A procedure for measuring overall severity of psychiatric disturbance. Archives of General Psychiatry, 33, 766-771.
67. Stewart, A. L., & Ware, J. E. (1992). Measuring functioning and well-being: The medical outcome study approach. Durham, NC: Duke University Press.
68. Weissman, M.M, & Bothwell, S. (1976). Assessment of social adjustment by patient self-report. Archives of General Psychiatry, 33, 1111-1115.
69. Spitzer, R.L., Williams, J.B.W., Gibbon, M., & First, M.B. (1990). Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II, Version 1.0). Washington, DC: American Psychiatric Press.
70. Costa, P.T., & McCrae, R.R. (1992). Normal personality inventories in clinical assessment: General requirements and potential for using the NEO Personality Inventory. Psychological Assessment, 4, 5-13.

84. Dohrenwend, B.S., Krasnoff, L., Askenasy, A.R., & Dohrenwend, B.P. (1978). Exemplification of a method for scaling life events: The PERI life events scale. Journal of Health and Social Behavior, 19, 205-229.
85. Coupland, N.J., Bell, C.J., & Potokar, J.P. (1996). Serotonin reuptake inhibitor withdrawal. Journal of Clinical Psychopharmacology, 16, 356-362.
86. Stahl, M.M., Linquist, M., Pettersson, M., Edwards, I.R., Sanderson, J.H., Taylor, N.F., Fletcher, A.P., & Schou, J.S. (1997). Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system. European Journal of Clinical Pharmacology, 53, 163-169.
87. Lejoyeux, M., & Ades, J. (1997). Antidepressant discontinuation: A review of the literature. Journal of Clinical Psychiatry, 58 (Suppl 7), 11-15.
88. Dinan, T.G. (1993). Lithium augmentation in sertraline-resistant depression: A preliminary dose-response study. Acta Psychiatrica Scandinavica, 88, 300-301.
89. Ontiveros, A., Fontaine, R., & Elie, R. (1991). Refractory depression: The addition of lithium to fluoxetine or desipramine. Acta Psychiatrica Scandinavica, 83, 188-192.
90. Meterissian, G.B., & Bradwejn, J. (1989). Comparative studies on the efficacy of psychotherapy, pharmacotherapy, and their combination in depression: Was adequate pharmacotherapy provided? Journal of Clinical Psychopharmacology, 9, 334-339.
91. Fawcett, J., Epstein, P., Fiester, S.J., Elkin, I., & Autry, J.H. (1987). Clinical Management-Imipramine/Placebo Administration Manual: NIMH Treatment of Depression Collaborative Research Program. Psychopharmacological Bulletin, 23, 309-324.
94. Kraemer, H.C., & Pruyn, J.P. (1990). The evaluation of different approaches to randomized clinical trials: Report on the 1987 MacArthur Network I Methodology Workshop. Archives of General Psychiatry, 12, 1163-1169.
95. Cohen, J., & Cohen, P. (1975). Applied multiple regression/correlation analysis for the behavioral sciences. New York: Erlbaum.
96. Cox, D. R. (1972). Regression models and life tables. Journal of the Royal Statistical Society, B, 34, 187-202.
97. Flick, S.N. (1988). Managing attrition in clinical research. Clinical Psychology Review, 8, 499-515.
98. Gibbons, R.D., Hedeker, D., Waternaux, C.M., & Davis, J.M. (1988). Random regression models: A comprehensive approach to the analysis of longitudinal psychiatric data. Psychopharmacology Bulletin, 24, 438-443.
99. Gibbons, R.D., Hedeker, D., Elkin, I., Waternaux, C., Kraemer, H.C., Greenhouse, J.B., Shea, M.T., Imber, S.D., Sotsky, S.M., & Watkins, J.T. (1993). Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Archives of General Psychiatry, 50, 739-750.
100. Greenhouse, J.B., Stangl, D., & Bromberg, J. (1989). An introduction to survival analysis: Statistical methods for analysis of clinical trial data. Journal of Consulting and Clinical Psychology, 57, 536-544.
101. Kaplan, E.L., & Meier, P. (1958). Nonparametric estimation from incomplete observations. Journal of the American Statistical Association, 53, 457-481.
102. Mantel, N. (1966). Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemotherapy Report, 50, 163-170.
103. Cohen, J. (1969). Statistical power analysis for the behavioral sciences. New York: Academic Press.
104. Jacobson, N.S., Follette, W.C., & Revenstorf, D. (1984). Psychotherapy outcome research: Methods for reporting variability and evaluating clinical significance. Behavior Therapy, 15, 336-352.
105. Freedman, L.S. (1982). Tables of the number of patients required in clinical trials using the logrank test. Statistics in Medicine, 1, 121-129.
106. Rounsaville, B.J., Weissman, M.M., & Prusoff, B.A. (1981). Psychotherapy with depressed outpatients: Patient and process variables as predictors of outcome. British Journal of Psychiatry, 138, 67-74.
107. Hollon, S.D., & Fawcett, J. (1995). Combined medication and psychotherapy. In G. Gabberd (Ed.), Treatments of psychiatric disorders (2nd ed., pp. 12221-1236). Washington, D.C.: American Psychiatric Press.