

Acupuncture for Depression: A Randomized Controlled Trial

John J. B. Allen, Ph.D.; Rosa N. Schnyer, L.Ac.;
Andrea S. Chambers, M.A.; Sabrina K. Hitt, Ph.D.;
Francisco A. Moreno, M.D.; and Rachel Manber, Ph.D.

Objective: To assess the efficacy of acupuncture as an intervention for major depressive disorder (MDD).

Method: Acupuncture was examined in 151 patients with MDD (DSM-IV) who were randomly assigned to 1 of 3 groups in a double-blind randomized controlled trial. The specific intervention involved Traditional Chinese Medicine (TCM)-style acupuncture with manual stimulation for depression; the control conditions consisted of (1) a nonspecific intervention using a comparable number of legitimate acupuncture points not specifically targeted to depressive symptoms and (2) a waitlist condition, which involved waiting without intervention for 8 weeks. After 8 weeks, all patients received the depression-specific acupuncture. Each 8-week intervention regimen consisted of 12 acupuncture sessions delivered in an acupuncturist's office in the community. The primary outcome measure was the 17-item Hamilton Rating Scale for Depression. The study was conducted from February 1998 to April 2002.

Results: Twenty patients terminated treatment before the completion of the 8-week intervention (13%) but not differentially by study group. Random regression models of the intent-to-treat sample revealed that although patients receiving acupuncture improved more than those awaiting intervention, no evidence of differential efficacy of the depression-specific over nonspecific intervention was found. Response rates in acupuncture-treated patients were relatively low after 8 weeks (22% and 39% for specific and nonspecific intervention groups, respectively), with the response rate after the entire 16-week trial reaching 50%.

Conclusion: Although TCM manual acupuncture is a well-tolerated intervention, results fail to support its efficacy as a monotherapy for MDD. It can't be ruled out that factors unique to the implementation of acupuncture in this research study may have limited the efficacy of interventions compared to those provided in naturalistic settings.

Clinical Trials Registration:
ClinicalTrials.gov identifier NCT00010517.
(*J Clin Psychiatry* 2006;67:1665-1673)

Received Feb. 23, 2006; accepted May 10, 2006. From the Departments of Psychology (Drs. Allen and Hitt and Mss. Schnyer and Chambers) and Psychiatry (Dr. Moreno), University of Arizona, Tucson; Stanford University, Stanford, Calif. (Dr. Manber); and the Osher Institute, Harvard Medical School, Boston, Mass. (Ms. Schnyer).

This research was supported, in part, by grants from the National Institutes of Health (R21 RR09492, R01 MH56965, and R01 AT00001).

Dr. Moreno is a consultant for and has received grant research support from Cyberonics and Forest and has received honoraria from and is a member of the speakers/advisory boards for Cyberonics, Forest, and Wyeth-Ayerst. Drs. Allen, Hitt, and Manber and Mss. Schnyer and Chambers report no additional financial or other relationships relevant to the subject of this article.

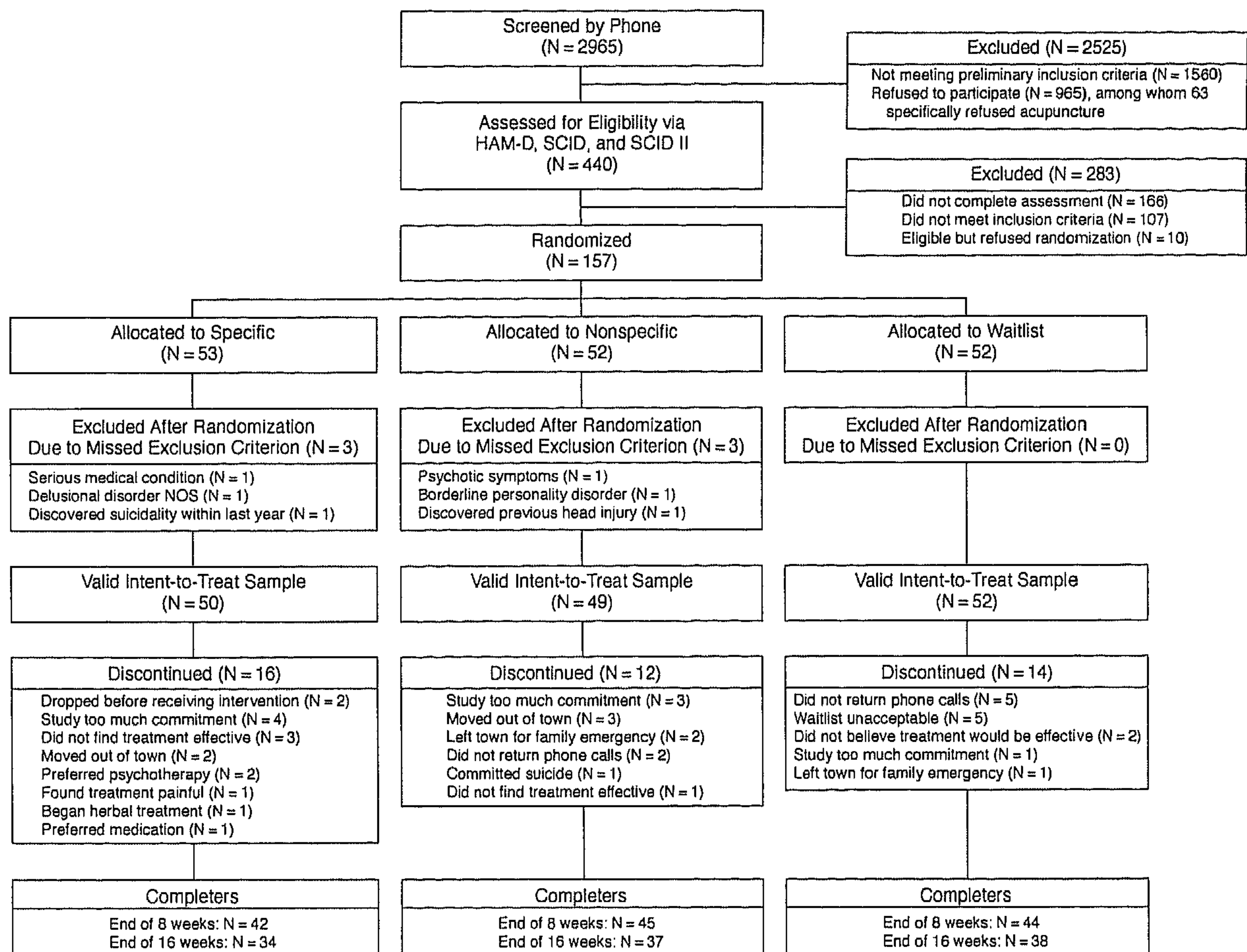
Acknowledgments are listed at the end of this article.

Corresponding author and reprints: John J. B. Allen, Ph.D., Department of Psychology, University of Arizona, P.O. Box 210068, Tucson, AZ 85721-0068 (e-mail: jallen@u.arizona.edu).

Major depressive disorder (MDD) is one of the most common problems for which people seek Complementary and Alternative Medicine (CAM) interventions.^{1,2} In 1 study,² nearly half of the depressed or anxious CAM users chose CAM instead of conventional medicine. Despite the frequency of CAM use among depressed persons, few randomized controlled trials have been conducted,³ but there are a number of modalities that hold promise.⁴

A number of studies⁵⁻¹⁶ and 1 double-blind randomized controlled trial¹⁷ suggest that acupuncture can be an effective monotherapy for the treatment of MDD and as an adjunct to pharmacotherapy.^{18,19} Most studies, however, did not carefully control for both practitioner and patient expectations, and were thus not double-blinded trials.

A small controlled double-blind study from our laboratory¹⁷ examined 38 female outpatients with major depressive disorder randomly assigned to 1 of 3 groups for 8 weeks: a group who received acupuncture that was specifically tailored for each individual's symptoms (Specific: SPEC), a group who received acupuncture that used legitimate acupuncture points but the interventions were not designed to treat symptoms of depression (Non-specific: NONSPEC), and a waitlist control. Upon completion of the initial 8 weeks, all clients received 8 weeks of the SPEC intervention. Those receiving the SPEC intervention had a significantly greater reduction in depressive symptoms than those receiving the NONSPEC intervention. There was also a trend towards a greater reduction

Figure 1. CONSORT²¹ Flowchart of Subject Screening and Enrollment

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, NOS = not otherwise specified, SCID = Structured Clinical Interview for DSM-IV, SCID II = Structured Clinical Interview for DSM-IV Axis II.

in depressive symptoms in those in the SPEC group compared with the waitlist, but the low sample size might have diminished the difference between the groups. The remission rate after all participants received the SPEC intervention (64%) was comparable to that of psychotherapy and medication trials, and the effects were maintained over 6 months for the majority of the participants.²⁰

Although those results were encouraging, this study was limited by the small sample size and by the specialized sample (younger women only). The current study sought to test the efficacy of acupuncture as a monotherapy for MDD in a large randomized controlled trial of both men and women with a range in the severity of MDD by comparing the efficacy of acupuncture intervention specifically designed to target each individual's depressive symptoms with an active valid acupuncture control that was not tailored to address an individual's symptoms of depression and with a waitlist control.

METHOD

Study Participants

From among 2965 prospective subjects who responded to newspaper advertisements between March 1998 and January 2002, 151 (104 women, 47 men) met study entry criteria and began acupuncture intervention or waitlist. Figure 1 provides a detailed flow chart summarizing study recruitment. Newspaper advertisements mentioned intervention for depression but not acupuncture. Patients aged 18 through 65 years were included if they met the DSM-IV²² diagnostic criteria for current MDD, assessed with the Structured Clinical Interview for DSM-IV (SCID-P²³), and had a score of 14 or greater on the 17-item Hamilton Rating Scale for Depression (HAM-D₁₇²⁴). Patients were excluded if any of the following were present: (1) dysthymia or chronic (> 2 years) MDD; (2) seasonal pattern; (3) any current Axis I diagnosis besides MDD or any Axis II Cluster B disorder; (4) history

Table 1. Synopsis of Intervention Details in Accordance With the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA²⁶)

Acupuncture rationale	TCM, individualized for each patient; assessment framework and treatment planning available in a published manual ²⁵
Needling details	Unilateral and bilateral points Number of needles ranged from 10 to 16 Depth of insertion: standard to each point according to TCM ²⁷ Responses elicited: de qi sensation Manual moderate stimulation Needles retained for 20 min Needle type: Carbo and Viva, Serins (for sensitive individuals); 36–38 (Chinese) gauge, 25–40 mm (body points), 15 mm (ear points)
Treatment regimen	Twice per week for 4 weeks, then once per week for 4 weeks for a given 8-week regimen
Co-intervention	None: no herbs, moxibustion, cupping, or advice regarding dietary or lifestyle modifications
Practitioner background	Training duration of at least 4 years In practice for at least 5 years NCCAOM board-certified
Control intervention: nonspecific acupuncture	Active comparison of valid acupuncture points intended to mimic a real acupuncture treatment Points needled as described above for specific intervention Participants blinded; patients instructed there are 2 approaches to treatment and that they will receive 1 approach Acupuncturists blinded to presence and nature of nonspecific treatments: told testing different styles of acupuncture for depression Justification of control provided in several sources ^{17,25,28,29}

Abbreviations: NCCAOM = National Certification Commission for Acupuncture and Oriental Medicine, TCM = Traditional Chinese Medicine.

of psychosis or mania; (5) substance abuse or dependence within the past 4 months; (6) any current relevant treatment; (7) endocrine abnormalities (e.g., hypothyroidism, unstable diabetes); (8) history of central nervous system involvement (e.g., seizures, brain injury, neurologic illness); (9) any medical disorder or treatment believed by the investigators to cause depression; (10) active suicidal risk necessitating immediate intervention or suicide attempt within the past year; or (11) pregnancy. From among the initial intent-to-treat sample of 151 subjects, 20 (13%) terminated prior to completion of the 8-week efficacy phase of the study, and 42 (28%) terminated prior to the completion of the entire 16-week study.

Prior to the administration of the SCID-P, all patients provided informed consent after the procedures and possible side effects were fully explained. All procedures were approved by the institutional review board at the University of Arizona.

Study Design

Factors other than acupuncture per se or the particular points selected can provide therapeutic impact. Such factors include, among others, the patient-acupuncturist relationship and actively engaging in activity believed to improve depression. The present design therefore utilized an active control for such nonspecific intervention effects, randomly assigning subjects to receive 1 of 2 types of acupuncture intervention or to a waitlist. Interventions individually tailored to treat each patient's specific symptoms of depression (SPEC intervention) were devised according to a standardized intervention manual,²⁵ and were based on the Traditional Chinese Medicine (TCM) style of acupuncture using manual stimulation. Full details of the intervention are in the manual,²⁵ and a synopsis

of the details of the intervention are presented in Table 1 in conformance to the standards for reporting interventions in controlled trials of acupuncture (STRICTA²⁶). Specific interventions were based on a TCM diagnostic and treatment framework using manual stimulation.²⁵

A placebo-like control intervention utilized a comparable number of valid acupuncture points that were not designed to treat the individual's depression (nonspecific intervention). The nonspecific (NONSPEC) intervention is an active intervention that utilized legitimate acupuncture points that were targeting the relief of symptoms believed to be unrelated to depression. As such, this nonspecific intervention is likely to have an effect greater than a truly inactive placebo intervention, and thus, the nonspecific intervention is an active comparator.

To control for the impact of acupuncturists' differential expectations on patients' expectation, an active nonspecific intervention was used, with the SPEC and NONSPEC interventions designed to appear similar to the patients—each involving points in the same general body regions. If SPEC interventions demonstrate greater efficacy than NONSPEC interventions, then the effect of acupuncture per se is presumed to be responsible.

The SPEC and NONSPEC intervention plans were developed by 1 of 3 assessing acupuncturists, and were administered by 1 of several other trained and board-certified acupuncturists (National Certification Commission for Acupuncture and Oriental Medicine: NCCAOM) who did not engage in intervention design. Because the nonspecific interventions involved valid acupuncture points, treating acupuncturists should perceive that they were providing a valid intervention, a belief that they would not have held if "sham" points had been used as a control. The treating acupuncturists were blind to experimental hypotheses and

Table 2. Demographic Variables by Treatment Group

Variable	SPEC (N = 49)	NONSPEC (N = 50)	WAIT (N = 52)
Age at onset, mean (SD), y	23.3 (11.4)	24.6 (12.8)	22.7 (14.0)
Age at intake, mean (SD), y	39.7 (9.9)	42.2 (10.6)	41.6 (12.5)
No. episodes, mean (SD)	6.9 (5.6)	5.8 (4.5)	7.0 (5.4)
HAM-D ₁₇ score, mean (SD)	22.1 (4.8)	22.0 (5.0)	22.8 (4.2)
BDI score, mean (SD)	28.0 (6.6)	28.7 (7.5)	28.7 (7.4)
Female, %	68	67	71
White, %	79	88	81

Abbreviations: BDI = Beck Depression Inventory.

HAM-D₁₇ = 17-item Hamilton Rating Scale for Depression.

NONSPEC = nonspecific acupuncture intervention (not designed to treat depression), SPEC = specific acupuncture intervention for depression, WAIT = waitlist control group.

the nature by which the SPEC and NONSPEC interventions were devised, and were not informed of which intervention plan they received. Acupuncturists were not told that the study would compare SPEC or NONSPEC treatments; rather, that the study would compare the efficacy of treatments for depression based on a number of different theoretical orientations. Nonetheless, it may not be appropriate to consider this study fully double-blind because it remains possible that the acupuncturists may have developed some awareness of the differences between the interventions. Patients were blind to intervention condition, as were raters who assessed outcome.

Patients were randomly assigned to 1 of 3 intervention groups following a stratified randomization schedule based on sex and severity of depression (HAM-D₁₇ score < 21 or ≥ 21): specific acupuncture intervention (N = 50), nonspecific acupuncture intervention (N = 49), or waitlist (N = 52). Randomization schedules were devised by the first author at study outset, with each client's assignment becoming known to the assessing acupuncturist and the study coordinator only after the completion of the intake assessment. Following the initial 8 weeks in 1 of these 3 intervention groups, all patients received SPEC intervention for the next 8 weeks. Each 8-week intervention regimen (both SPEC and NONSPEC) comprised 12 acupuncture sessions delivered in an acupuncturist's office in the community. Two sessions were given each week for the first 4 weeks followed by 1 per week thereafter. The first 8-week intervention phase is of primary interest to test whether acupuncture may hold efficacy in the treatment of depression. The second 8-week phase was devised to ethically provide all patients with the intervention hypothesized to be most effective, and also to allow for the possibility to examine dose-response effects.

Evaluations and Outcome Measures

The primary outcome measure was the HAM-D₁₇,²⁴ administered at intake and at 4-week intervals thereafter by trained raters blind to intervention condition. An intraclass correlation of 0.97 was obtained for a sample

of 30 interviews comparing the original interviewers' HAM-D₁₇ scores with those of other interviewers (original interviewer excluded). At weekly intervals all patients completed a secondary outcome measure, the Beck Depression Inventory (BDI),²⁵ to provide a weekly index of depression severity.

Data Management and Analysis

All data were double-entered and checked for consistency prior to analysis. Response was defined a priori as a 50% or larger reduction following intervention in the HAM-D₁₇ score, whereas remission was defined jointly by a final HAM-D₁₇ score of less than 7 and at least a 50% reduction in HAM-D₁₇ score from intake. Remission and response were defined based on a comparison of the intake HAM-D₁₇ score to the last available observation in cases where subjects terminated prematurely.

Change in depression severity over time was examined using random regression analyses^{31,32} using a mixed effects linear regression model with MIXREG software (Version 1.2³²). The model focused on the first 8-week phase to compare the rate of change across the 3 intervention groups (SPEC, NONSPEC, and waitlist). The random regression approach utilizes all available data, estimating rate of change for each subject based on extant observations. The first 8 weeks included 3 HAM-D₁₇ assessments (baseline, end of week 4, end of week 8), and 10 BDI assessments (baseline, 1 per week for 8 weeks, and 1 at the end of week 8 coincident with the HAM-D₁₇ assessment).

RESULTS

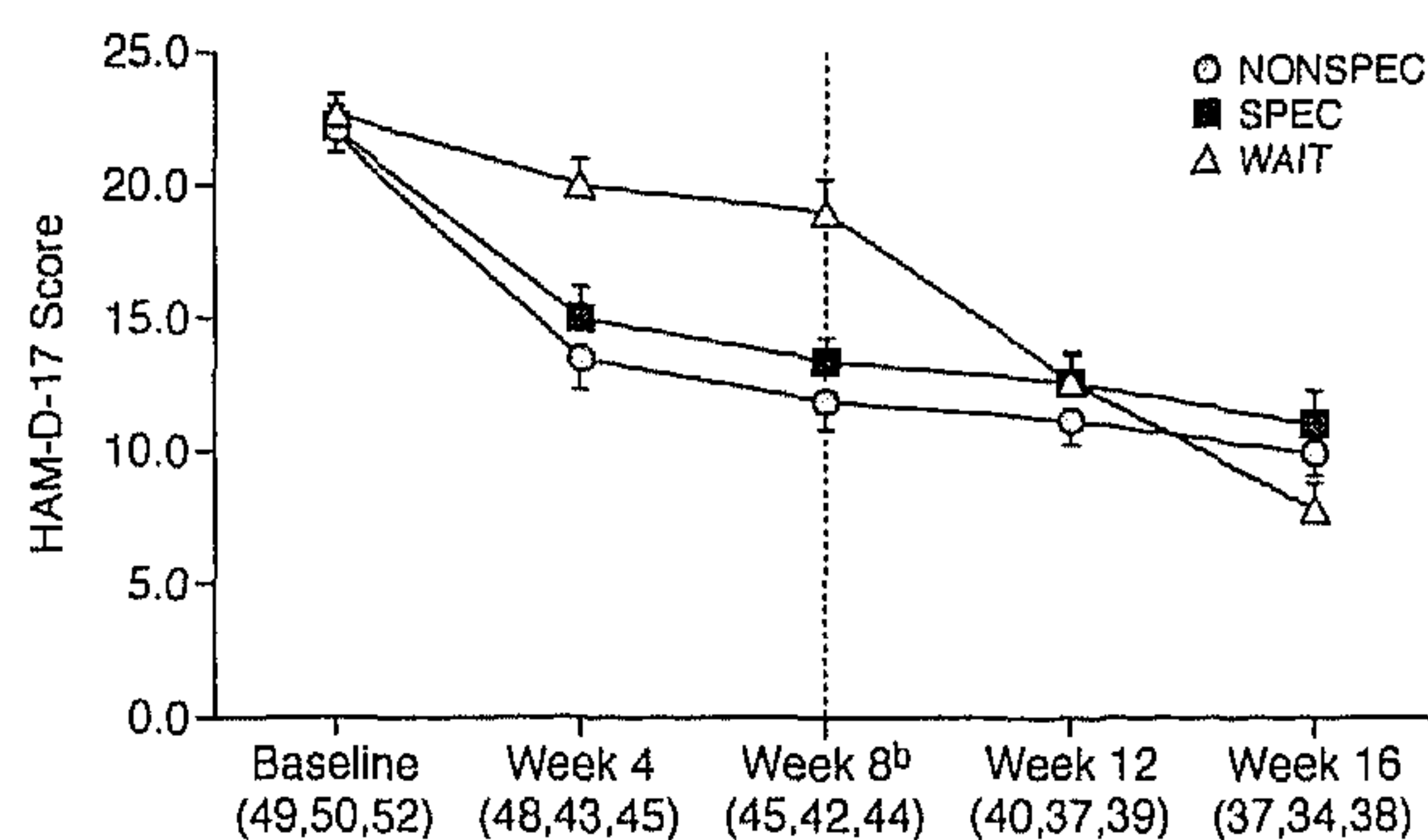
Sample Features

Table 2 presents demographic and symptom data at intake for patients, separately for each intervention group. No significant differences emerged between intervention groups with respect to age, male/female ratio, ethnicity, age at onset, number of previous episodes, or symptom severity as assessed by the HAM-D₁₇ or the BDI. Collapsed across intervention groups, the sample was 69% female with a mean ± SD age of 41.2 ± 11.0 years. The sample had mild to moderate depression (HAM-D₁₇ score = 22.3 ± 4.6), with the typical patient having 6.6 ± 5.2 previous episodes of MDD, with a mean age at onset of 23.5 ± 12.7 years.

Symptom Outcome

The primary analyses focused on the comparative outcome across the first 8 weeks of intervention, the time during which patients were randomly assigned to receive SPEC or NONSPEC acupuncture intervention or to waitlist. Data from the second 8-week phase, during which all patients received SPEC acupuncture, are of secondary interest and are presented to address whether a

Figure 2. Mean (\pm SE) 17-Item Hamilton Rating Scale for Depression Scores by Intervention Group Over Time^a



^aNumbers in parentheses below each week indicates the number of patients providing data at that week for the nonspecific, specific, and waitlist groups, respectively.

^bFollowing the week 8 assessment, all patients received the specific acupuncture intervention.

Abbreviations: HAM-D-17 = Hamilton Rating Scale for Depression, NONSPEC = nonspecific acupuncture intervention (not designed to treat depression), SPEC = specific acupuncture intervention for depression, WAIT = waitlist control group.

longer duration of intervention would result in a better clinical response.

Hamilton Rating Scale for Depression. Random regression analysis of HAM-D₁₇ data across the first 8 weeks of intervention revealed a significant decrease in depression severity across all subjects ($z = -11.2$, $p < .001$), but with the rate of change varying by group ($z = 4.4$, $p < .001$). When groups were compared with one another, greater decreases in severity were exhibited by both the SPEC ($z = 3.5$, $p < .001$) and NONSPEC ($z = 4.3$, $p < .001$) groups compared with the waitlist group, but the SPEC and NONSPEC groups did not differ in rate of change from one another ($z = 1.1$, $p > .2$). Figure 2 depicts HAM-D₁₇ scores by intervention group over time.

To examine whether an extended duration of intervention resulted in differential improvement, all subjects were compared at week 16 in a random regression model examining HAM-D₁₇ scores at intake and study completion. If symptom change differs by group, it may reflect the extended impact of acupuncture generally, in which case the 2 intervention groups should demonstrate greater improvement than the waitlist group. Alternatively, it could reflect the extended impact of the SPEC acupuncture intervention in particular, in which case patients in the SPEC group should show the greatest improvement as they would be the only group to receive up to 16 weeks of SPEC acupuncture intervention, with the NONSPEC intervention group and waitlist group each only receiving up to 8 weeks of SPEC intervention. As expected, the random regression analysis revealed a significant decrease in depression severity across all subjects ($z = -9.8$, $p < .001$), but with the rate of change not varying by group ($z = -1.7$, NS [not significant]). Descriptively, the waitlist group,

with the fewest sessions of intervention, in fact had the lowest final depression severity.

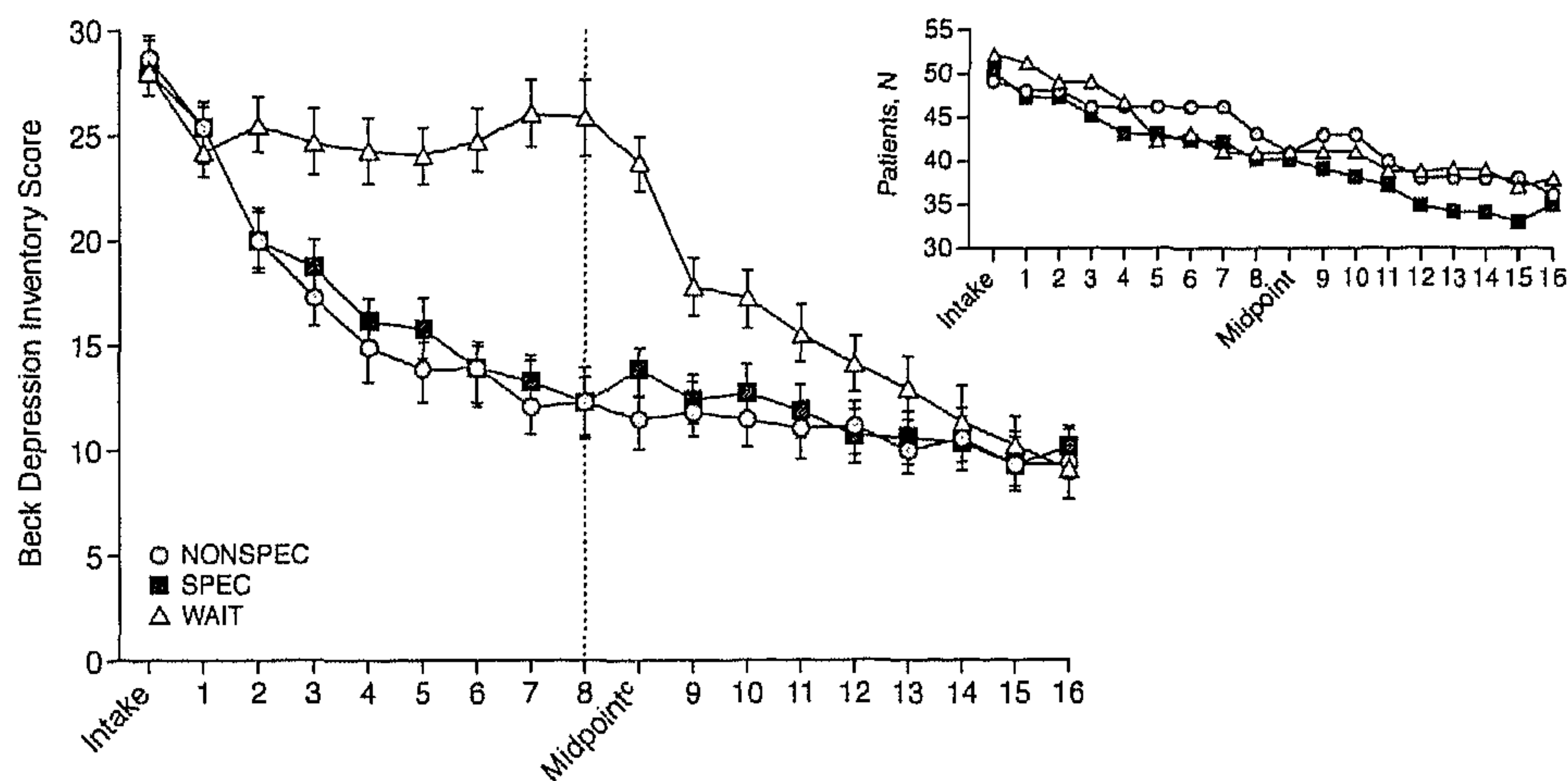
Beck Depression Inventory. Random regression analysis of BDI scores across the first 8 weeks of intervention revealed a significant decrease in depression severity across all subjects ($z = -13.6$, $p < .001$), but with the rate of change varying by group ($z = 6.8$, $p < .001$). When groups were compared with one another, greater decreases in severity were exhibited by both the SPEC ($z = 6.1$, $p < .001$) and NONSPEC ($z = 6.6$, $p < .001$) groups compared with the waitlist group, but the SPEC and NONSPEC groups did not differ in rate of change from one another ($z = 1.3$, $p > .17$). Figure 3 depicts BDI scores by intervention group over time.

BDI data from the conclusion of the study were examined to again assess whether an extended duration of intervention resulted in differential improvement. The random regression model examining BDI scores between all subject groups at intake and study completion revealed as expected a significant decrease in depression severity across all subjects ($z = -14.6$, $p < .001$), but with the rate of change not varying by group ($z = -0.1$, NS).

Response and remission rates. Response and remission rates, depicted in Figure 4, were compared using χ^2 tests. Response rates after 8 weeks of intervention were low: SPEC intervention, 22% (11/50); NONSPEC intervention, 39% (19/49); and waitlist, 17% (9/52) ($\chi^2 = 6.6$, $N = 151$, $p < .05$). Remission rates for SPEC, NONSPEC, and waitlist patients were 16% (8/50), 33% (16/49), and 8% (4/52), respectively ($\chi^2 = 10.7$, $N = 151$, $p < .01$). Follow-up analyses revealed that, whereas response and remission rates for those receiving NONSPEC acupuncture were significantly higher than waitlisted patients (response: $\chi^2 = 5.8$, $N = 101$, $p < .05$; remission: $\chi^2 = 9.9$, $N = 101$, $p < .01$), rates did not differ between those receiving SPEC intervention and those receiving waitlist (response: $\chi^2 = 0.4$, $N = 102$, NS; remission: $\chi^2 = 1.7$, $N = 102$, NS). There were trends for response and remission rates to be higher among those receiving NONSPEC compared with SPEC intervention (response: $\chi^2 = 3.3$, $N = 99$, $p < .07$; remission: $\chi^2 = 3.7$, $N = 99$, $p < .06$).

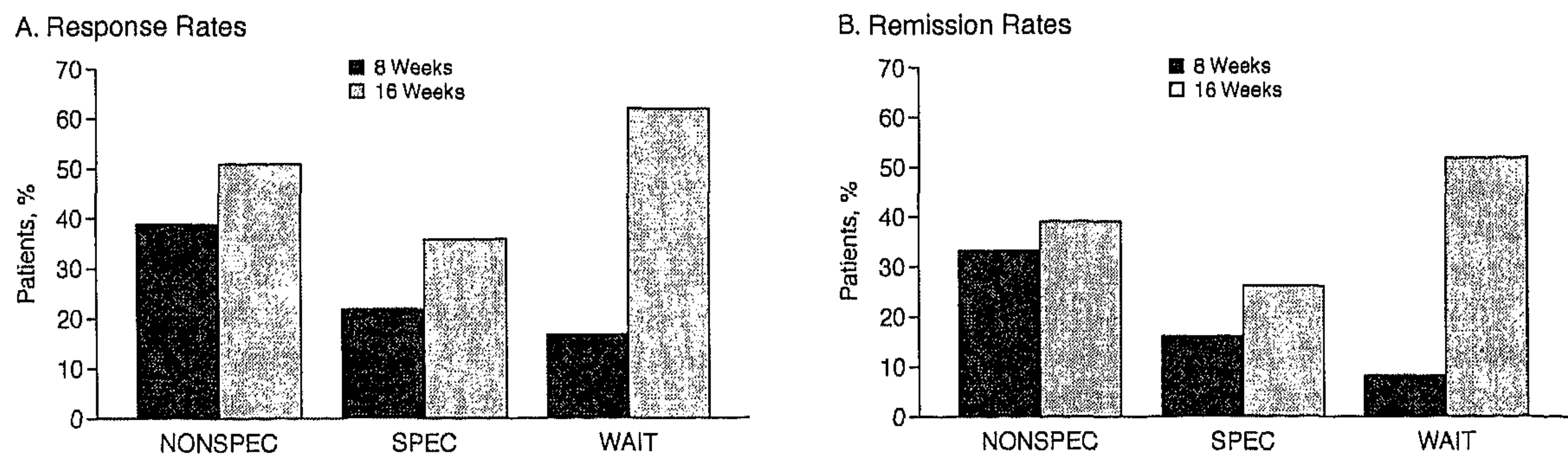
Following 16 weeks of intervention, 50% of the entire sample had experienced a response, with 39% experiencing remission. Response rates were compared by group after patients in the SPEC intervention group had received up to 16 weeks of SPEC intervention and patients in the other groups received up to 8 weeks of SPEC intervention following either NONSPEC intervention or waitlist. Overall response rates for each group were higher than after 8 weeks: SPEC intervention, 36% (18/50); NONSPEC intervention, 51% (25/49); and waitlist, 62% (32/52) ($\chi^2 = 6.7$, $N = 151$, $p < .05$). Remission rates for SPEC, NONSPEC, and waitlist patients were 26% (13/50), 39% (19/49), and 52% (27/52), respectively ($\chi^2 = 7.2$, $N = 151$, $p < .05$). Follow-up analyses revealed that response and

Figure 3. Mean (\pm SE) Beck Depression Inventory Scores by Intervention Group Over Time^{a,b}



^aInset at upper right depicts the number of patients providing data at that week for the nonspecific, specific, and waitlist groups.
^bAssessments 1–8 and 9–16 were completed at the intervention session (or at home for waitlist clients); Intake and midpoint assessments were completed during the assessment visit that included the HAM-D₁₇.
^cFollowing the midpoint assessment, all patients received the specific acupuncture intervention.
 Abbreviations: NONSPEC = nonspecific acupuncture intervention (not designed to treat depression), SPEC = specific acupuncture intervention for depression, WAIT = waitlist control group.

Figure 4. Response and Remission Rates by Group After 8 Weeks and After 16 Weeks of Intervention^a



^aFollowing the 8-week assessment, all patients received the specific acupuncture intervention.
 Abbreviations: NONSPEC = nonspecific acupuncture intervention (not designed to treat depression), SPEC = specific acupuncture intervention for depression, WAIT = waitlist control group.

remission rates for those receiving NONSPEC acupuncture did not differ significantly from the rates of patients waitlisted prior to SPEC intervention or from the rates of those receiving 16 weeks of SPEC intervention. Those receiving 16 weeks of SPEC intervention, however, had significantly lower response and remission rates than those patients who were first waitlisted (response: $\chi^2 = 6.7$, $N = 102$, $p < .05$; remission: $\chi^2 = 7.2$, $N = 102$, $p < .01$).

Adverse Events

Adverse events were assessed weekly for all subjects receiving intervention, utilizing a form inquiring specifically about changes in symptoms, new symptoms, or per-

ceived side effects of acupuncture, as well as open-ended reports of negative events. Tallies of events in specific categories (from COSTART³³) were then totaled. During the 8-week intervention, participants in the SPEC and NONSPEC intervention groups experienced comparable numbers of adverse events (no χ^2 test was significant for group differences in rates of reported symptoms listed in Table 3). Only 5 patients specifically reported needle-related pain, 1 of whom discontinued prematurely because of the needle pain.

It is unclear to what extent the adverse events reported by participants receiving the interventions are due to the acupuncture per se or to what extent some symptoms

Table 3. Patients Reporting Adverse Events During 8-Week Acupuncture Intervention by Group, %

Category	SPEC (N = 50)	NONSPEC (N = 49)
Somatic symptoms ^a	62	63
Pain symptoms	26	18
Intensification of sleep difficulties	20	20
Intensification of emotions/ emotional reactions	18	18
Unusual perceptual experiences	12	4
Miscellaneous	4	10
Intervention error ^b	2	0
Suicide	0	2
Indicated at least 1 of the above	62	65

^aIncludes COSTART²⁹ categories of nervous tension, muscle twitch, irregularity of heart beat, heartburn, flatulence, burping, appetite decrease, urination frequency changes, gastroesophageal reflux, exaggerated appetite, and weight increase.

^bSuch errors include retaining needles in a participant for an extended duration and leaving a participant in an acupuncturist's office after closing.

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms, NONSPEC = nonspecific acupuncture intervention (not designed to treat depression), SPEC = specific acupuncture intervention for depression.

(e.g., sleep problems) can be attributed to an intensification of depression symptoms. Unfortunately, adverse event tracking was not systematically collected on a weekly basis until the waitlisted participants began to receive treatment.

Assessment of Expectations

The extent to which blinding was successful was assessed by asking acupuncturists to rate expectations of outcome during the first 2 weeks of intervention. The decision to restrict these assessments to these weeks reflects that after the first few acupuncture sessions, differential intervention impact could drive differential expectations, with clients who show some overt signs of response influencing the acupuncturists' expectations for improvement. Treating acupuncturists were asked to rate 3 items concerning expectations for the client following the first session and again after the third session (at the start of the second week). Each of the following items was rated on a 5-point Likert scale: "How effective is this treatment for this client?" "How likely is it that you will be able to help this client using this treatment?" and "How much do you expect this client to improve by the end of this 8 week phase of treatment?" These 3 items were summed to produce a score that ranged from 3 to 15, and the resultant 3-item scale had good internal consistency reliability, with a Cronbach α of .91.

Expectations were assessed in a 2 (week) by 2 (intervention group) repeated-measures analysis of variance for the 92 subjects with complete data at each assessment point (46 SPEC, 46 NONSPEC). A main effect of time ($F = 5.4$, $df = 1,90$; $p < .05$) revealed that expectations (mean \pm SD) rose modestly from week 1 (11.2 ± 2.6) to

week 2 (11.6 ± 2.6), and a main effect of group ($F = 5.1$, $df = 1,90$; $p < .05$) indicated that acupuncturists had higher expectations for subjects receiving SPEC intervention (12.0 ± 2.5) than for those receiving NONSPEC intervention (10.8 ± 2.5). There was no interaction between intervention group and time in terms of acupuncturists' expectations ($F = 0.1$, $df = 1,90$; NS). Thus, although there were not large differences in the expectations of acupuncture providers as a function of intervention group, these results suggest that providers believed that SPEC interventions were slightly more likely to be effective than NONSPEC interventions.

Moderators of Intervention Outcome

Although the sample as a whole showed little evidence to suggest that SPEC acupuncture produced better response than NONSPEC acupuncture, several analyses were conducted to explore whether SPEC acupuncture may have efficacy for subjects with particular characteristics. For all analyses, a mixed-effects linear regression model with MIXREG software (Version 1.2³²) examined HAM-D₁₇ scores for the first 8-week phase, when subjects were assigned to SPEC or NONSPEC intervention or to waitlist. Candidate moderator variables were entered into an intervention group (SPEC, NONSPEC, waitlist) by time (intake, 4 weeks, 8 weeks) by moderator model. Candidate moderators included initial severity as assessed by the HAM-D₁₇, a history of chronicity, age at onset, current age, sex, and assessing acupuncturist. In no case did the interaction with the moderator reach significance, thus providing no support for the possibility that acupuncture has efficacy for a subset of depressed individuals.

Expectations

In order to determine whether acupuncturists' expectations could explain symptom improvement, individual regressions estimated individual slopes for each participant's change in symptoms as measured by the HAM-D₁₇ and BDI scores across the first 8 weeks of SPEC and NONSPEC intervention. Before individuals' slopes were calculated, regressions that modeled different change trajectories (e.g., linear vs. quadratic) were compared to determine which model of time could best estimate symptom scores across the 8 weeks of intervention. The linear model provided the best fit in comparison with other growth trajectory regressions for estimating change in HAM-D₁₇ and BDI scores ($R^2 = 0.23$ and 0.24 , respectively). These linear regressions of time predicting symptom change estimated the slope for each individual.

Acupuncturists' expectations for intervention success were measured during the first and third acupuncture session. Because these 2 measures were highly correlated ($r = 0.87$, $p < .001$), the mean was calculated and used in the subsequent analyses. Acupuncturists' expectations were unrelated to HAM-D₁₇ slopes (Pearson $r = 0.11$,

$p = .32$), to BDI slopes (Pearson $r = 0.00$, $p = 1.0$), or to response or remission status (Kendall τ -b $r = -0.01$, $p = .93$ and $r = -0.03$, $p = .767$, respectively).

DISCUSSION

The results of this randomized controlled trial of acupuncture as an intervention for depression indicate that although patients receiving acupuncture demonstrated significantly greater improvement than patients assigned to waitlist, there was no evidence to support differential efficacy of the 2 types of acupuncture intervention. Interventions designed to specifically target depression resulted in no better outcome than those designed to serve as a control intervention. Such results could reflect that the SPEC acupuncture intervention was not particularly effective, or that the intended control of NONSPEC acupuncture was somewhat more effective than predicted, or both. The relatively low response rates suggest that implementation of the SPEC acupuncture intervention in this study was not particularly effective, the reasons for which are considered below. The unexpected trend for response rates to be higher in the NONSPEC control intervention than in the SPEC acupuncture intervention also argues for the possibility that the NONSPEC intervention may have produced greater impact than intended. Finally, differences in provider expectations between SPEC and NONSPEC interventions, although small in magnitude, were statistically significant, suggesting that the blinding strategy was not entirely successful. Nonetheless, no evidence that acupuncturists' expectations influenced clinical outcome emerged.

Consideration of the TCM-Based Interventions

A consideration of these interventions from the perspective of TCM would support both the possibility that the SPEC intervention was suboptimal and the possibility that the NONSPEC intervention was a rather active control intervention. The biophysiologic mechanism of action of acupuncture is not yet well understood,³⁴ nor is there sufficient information regarding site specificity of acupuncture points or differences in needle manipulation, 2 principal features that underlie TCM acupuncture.³⁵ Clinically, differences in point selection and needle stimulation among practitioners are determined by training, style of intervention, experience, and personal preference. Points believed to have a direct effect on a particular condition are intrinsically related to other less direct or "specific" points. Because a principal aim of this study was to maintain blinding of the acupuncture providers, an active control was selected that consisted of nonspecific but valid acupuncture points. These points were distributed in a well-balanced fashion along the surface of the body and stimulated with effective needle manipulation. Beyond these effects, the SPEC acupuncture intervention consisted

of acupuncture points that were believed to directly address the individual's depression presentation according to this TCM style intervention. Both SPEC and NONSPEC points, however, are traditionally believed to have systemic regulatory effects; NONSPEC points were not chosen because of limited, localized action, and they have the potential for system-wide effects. Thus in assessing intervention efficacy in depression, NONSPEC valid acupuncture points may provide an active and potentially therapeutic control, one that may be difficult for SPEC interventions to exceed.

It is also possible that factors necessary for the controls in this study reduced the potential effectiveness of SPEC acupuncture. In naturalistic practice, continuous nonverbal feedback from the patient is used by the practitioner to design and modify the intervention. Separating the assessor from the treatment provider in an interactive intervention such as acupuncture may have compromised the ability of the assessors to design and of the practitioners to provide effective intervention. Whether the present implementation's lack of ecological validity may have influenced the findings remains an empirical question, one that could only be addressed in a study comparing response using more naturalistic modes of assessment and intervention delivery.

Another factor that may have limited the success of the SPEC intervention concerns the extent to which the assessors and intervention providers adequately implemented the protocols detailed in the manual.²⁵ Although we provided training to our assessors on the use of our manualized approach to intervention, and case consultation occurred on a subset of the cases, the study did not include supervision of every assessment to assure compliance. Furthermore, the design of the study assumed that intervention providers with a variety of backgrounds, levels of training, and experience were interchangeable and did not conduct systematic quality control of intervention implementation beyond tracking that the appropriate needles had been reported to be used at each session.

It remains possible that specificity of acupuncture points for depression is not evident in clinical outcome measures but that other changes may unfold differently over time for those receiving SPEC and NONSPEC acupuncture.^{28,36} Unfortunately, the present design does not allow for testing this possibility, as all subjects subsequently received SPEC acupuncture, and long-term follow-up data were not obtained for nonresponders.

Implications

The overall low response rate achieved with acupuncture suggests that TCM-style acupuncture with manual stimulation is not likely to be an adequate monotherapy for many with depression. Clinically, TCM acupuncture is often commonly combined with adjunctive techniques (moxibustion, cupping), Chinese herbs, and patient edu-

cation. In many cases, patients seek acupuncture to enhance psychotherapy or medication.

The low response rate seen in this study contrasts with 2 other studies conducted by this research team. In a preliminary study of 38 women,¹⁷ patients receiving SPEC acupuncture had a significantly better response than those receiving NONSPEC, with 50% of those receiving SPEC intervention and 27% of those receiving NONSPEC intervention experiencing remission following an 8-week intervention. Similarly, a study of depression during pregnancy²⁸ found that 69% of those receiving SPEC intervention and 47% of those receiving NONSPEC intervention experienced remission following an 8-week intervention. Although both samples involved only women of younger age, moderator analyses failed to provide support for the possibility that SPEC and NONSPEC acupuncture were differentially effective for women of childbearing age in the present study. Other demographic factors that may have differed between the present study and these previous studies, such as history of chronicity, also failed to moderate the pattern of results. Depression during pregnancy²⁸ may be mediated by hormonal changes that increase vulnerability to depression³⁷; these changes may respond differently to acupuncture.

Acknowledgments: The authors thank A. John Rush, M.D., for his kind consultations; Leslie McGee, Dipl.Ac.; Cathy Travis, Dipl.Ac.; Sandra Gallagher, Ph.D.; and Keo Taitano, Ph.D., for their assistance with assessing patients in this study; the numerous acupuncturists who provided the many treatments; and the many research assistants who assisted in the administrative tasks.

REFERENCES

- Astin JA. Why patients use alternative medicine: results of a national study. *JAMA* 1998;279:1548-1553
- Unutzer J, Klap R, Sturm R, et al. Mental disorders and the use of alternative medicine: results from a national survey. *Am J Psychiatry* 2000;157:1851-1857
- Ernst E, Rand JJ, Stevinson C. Complementary therapies for depression: an overview. *Arch Gen Psychiatry* 1998;55:1026-1032
- Manber R, Allen JJB, Morris MM. Alternative treatments for depression: Empirical support and relevance to women. *J Clin Psychiatry* 2002;63:628-640
- Chengying Y. Mind-regulating acupuncture treatment of neurosis, using points of Du channel. *Int J Clin Acupuncture* 1992;3:193-196
- Cherkezova M, Toteva S. Acupuncture in the treatment of alcoholics with a depressive syndrome. *J Russ East Eur Psychiatry* 1993;26:28-30. Abstract from: OVID File: PsychINFO Update Code: 19940101 Number: 19941994 19902905 19940001
- Dudaeva KI, Mikhailova ES, Poliakov SE. Neurophysiologic changes during the treatment of endogenous depression by reflexotherapy. *Zh Nevropatoli Psikhiatr Im S S Korsakova* 1990;90:99-103. Abstract from: OVID File: PsychINFO Update Code: 19910401 Number: 1991 73037 001
- Frydrychowski A, Landowski J, Watrobski Z, et al. An attempt at applying acupuncture in the treatment of depressive syndromes. *Psychiatria Polska* 1984;18:247-250. Abstract from: OVID File: PsychINFO Update Code: 19860601 Number: 19861986 19815230 19860001
- Luo HC, Jia YK, Li Z. Electro-acupuncture vs amitriptyline in the treatment of depressive states. *J Tradit Chin Med* 1985;5:3-8
- Luo HC, Jia YK, Wu XH, et al. Electro-acupuncture in the treatment of depressive psychosis. *Int J Clin Acupuncture* 1990;1:7-13
- Han JS. Electroacupuncture: an alternative to antidepressants for treating affective diseases? *Int J Neurosci* 1986;29:79-92
- Polyakov SE. Acupuncture in the treatment of endogenous depressions. *Soviet Neurology & Psychiatry* 1988;21:36-44
- Suobin K. Clinical observation on 103 cases of neurasthenia treated with plum-blossom needle tapping. *Int J Clin Acupuncture* 1991;2:419-421
- Yang X. Clinical observation on needling extra channel points in treating mental depression. *J Tradit Chin Med* 1994;14:14-18
- Han C, Li XW, Luo HC. Comparative study of electro-acupuncture and maprotiline in treating depression. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2002;22:512-514, 521
- Han C, Li X, Luo H, et al. Clinical study on electro-acupuncture treatment for 30 cases of mental depression. *J Tradit Chin Med* 2004;24:172-176
- Allen JJB, Schnyer RN, Hitt SK. The efficacy of acupuncture in the treatment of major depression in women. *Psychol Sci* 1998;9:397-401
- Roschke J, Wolf C, Muller MJ, et al. The benefit from whole body acupuncture in major depression. *J Affect Disord* 2000;57:73-81
- Luo HC, Shen YC, Jia YK. Clinical study of electro-acupuncture on 133 patients with depression in comparison with tricyclic amitriptyline. *Chin J Modern Developments Tradit Chin Med* 1998;8:77-80, 68
- Gallagher SM, Allen JJB, Hitt SK, et al. Six-month depression relapse rates among women treated with acupuncture. *Complement Ther Med* 2001;9:216-218
- Moher D, Schulz KF, Altman D, et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;285:1987-1991
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994
- First MB, Spitzer RL, Gibbon MG, et al. *The Structured Clinical Interview for DSM-IV*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 1994
- Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278-296
- Schnyer RN, Allen JJB, Manber R, et al. *Acupuncture in the Treatment of Major Depression: A Manual for Research and Practice*. London, United Kingdom: Harcourt-Brace Churchill Livingstone; 2001
- MacPherson H, White A, Cummings M, et al. Standards for reporting interventions in controlled trials of acupuncture: The STRICTA recommendations. *J Altern Complement Med* 2002;8:85-89
- Bensky D, O'Connor J, eds. *Acupuncture: A Comprehensive Text*. Shanghai College of TCM. Vista, CA: Eastland Press; 2003
- Manber R, Schnyer RN, Allen JJ, et al. Acupuncture: a promising treatment for depression during pregnancy. *J Affect Disord* 2004;83:89-95
- Schnyer RN, Allen JJ. Bridging the gap in complementary and alternative medicine research: manualization as a means of promoting standardization and flexibility of treatment in clinical trials of acupuncture. *J Altern Complement Med* 2002;8:623-634
- Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-571
- Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data: application to the NIMH treatment of Depression Collaborative Research Program dataset. *Arch Gen Psychiatry* 1993;50:739-750
- Hedeker D, Gibbons RD. MIXREG: a computer program for mixed-effects regression analysis with autocorrelated errors. *Comput Methods Programs Biomed* 1996;49:229-252
- U.S. Food and Drug Administration. *COSTART: Coding Symbols for Thesaurus of Adverse Reaction Terms*. 5th ed. Rockville, Md: U.S. Department Health Human Services, Center for Drug Evaluation and Research, Food and Drug Administration, Center for Drugs and Biologics; 1995
- Hammerschlag R, Lao L. Future directions for research on the physiology of acupuncture. In: Stux G, Hammerschlag R, eds. *Clinical Acupuncture: Scientific Basis*. Heidelberg, Germany: Springer; 2000:211-220
- Zaslowski CJ, Cobbin D, Lidums E, et al. The impact of site specificity and needle manipulation on changes to pain pressure threshold following manual acupuncture: a controlled study. *Complement Ther Med* 2003; 11:11-21
- Bensoussan A, Talley NJ, Hing M, et al. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. *JAMA* 1998;280:1585-1589
- Joffe H, Cohen L. Estrogen, serotonin, and mood disturbance: where is the therapeutic bridge? *Biol Psychiatry* 1998;44:798-811