The Safety, Acceptability, and Effectiveness of Acupuncture as an Adjunctive Treatment for Acute Symptoms in Bipolar Disorder

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Objective: There is growing interest in the utility of nonpharmacologic treatments for mood symptoms, including mood elevation and depression associated with bipolar disorders. The purpose of this research was to provide preliminary data on the safety, effectiveness, and acceptability of adjunctive acupuncture in the acute treatment of hypomania and depression associated with bipolar disorder.

Method: Two randomized trials were conducted to assess the benefits of adjunctive acupuncture for symptoms of depression and hypomania in patients with bipolar disorder (DSM-IV criteria). For 20 patients experiencing symptoms of hypomania, targeted acupuncture (points specific to symptoms) was compared to acupuncture points off the acupuncture meridian over 12 weeks (from May 2000 through May 2003). For patients experiencing symptoms of depression (n = 26), targeted acupuncture was compared to acupuncture for nonpsychiatric health concerns over 8 weeks (from November 2001 through May 2003). Preexisting psychotropic medications were maintained at stable doses throughout study participation.

Results: Regardless of acupuncture assignment or symptom pattern at entry, all patients experienced improvement over the course of study participation. There was evidence that acupuncture treatment did target the symptom dimension of interest (mood elevation in Study I, depression in Study II). There were few negative side effects and no attrition directly associated with adjunctive acupuncture.

Conclusions: Novel methodologies are needed to assess the utility of acupuncture as adjunctive treatment of mood episodes associated with bipolar disorder. We observed similar benefits associated with "placebo" acupuncture experiences and active treatment. Further studies are warranted.

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Bipolar disorder is a severe and chronic mood disorder affecting over 3.9% of the U.S. population.[1] The severe and persistent nature of the illness, limited treatment response to standard monotherapy, and frequent need for medication combinations that can incur significant side effects create conditions in which nonmedication treatment options may be welcome. There is evidence that patients are increasingly interested in complementary and alternative medicine (CAM) for emotional and psychiatric conditions, including major depressive disorder (MDD) and bipolar disorder.[2–6]

Acupuncture involves stimulation of specific locations on the skin or acupuncture points by a variety of techniques.[7] Traditionally, acupuncture stimulation is thought to regulate a functional network of interconnected channels, with the purpose of correcting dysfunction, restoring adaptability, and regaining balance. In terms of Western science, a hypothesized mechanism for the putative effect of acupuncture in depression is that it may be a physiologic means to activate the endogenous monoamine system in the central nervous system.[8] Functional

impairment of monoamine neurotransmitters and related cellular systems in the brain have been suggested as an etiologic factor for affective disorders, and acupuncture and electroacupuncture have been shown to stimulate the synthesis and release of the monoamines serotonin and norepinephrine in animals.[8,9] Additionally, studies suggest that acupuncture needling procedures increase levels of endorphins,[10] another putative mechanism for acupuncture effect in depression.[11]

Most research to date has focused on the use of acupuncture for unipolar depression (MDD). Acupuncture treatments developed specifically for depression have been compared to acupuncture targeted to other conditions (nonspecific to treat depression), massage as an active control, or to a wait-list control condition. Two studies found targeted acupuncture significantly better than an active control (acupuncture targeted for symptoms other than depression),[12,13] while the third, the largest of these studies, found that both acupuncture targeted to depression and acupuncture targeted to other symptoms were equally effective in reducing depression compared to a wait-list control.[14] These randomized trials provide preliminary and inconclusive evidence for the effectiveness of monotherapy acupuncture in the treatment of clinical depression.

Several trials have also examined the efficacy of acupuncture compared to antidepressant treatment. Electroacupuncture treatment was compared to maprotiline (a tetracyclic antidepressant that inhibits the reuptake of norepinephrine) (N = 61), and both groups improved, but no significant between-group differences were observed.[15] Two randomized, controlled trials comparing the effects of electroacupuncture and the tricyclic antidepressant amitriptyline hydrochloride in depressed patients found that both groups experienced a reduction in depression rating scores with no between-group differences.[16,17] In these reports, the acupuncture groups experienced fewer side effects.

One trial examined the utility of adjunctive acupuncture for treatment of depression. A single-blind, placebo-controlled study comparing targeted acupuncture plus antidepressant, nonmeridian acupuncture plus antidepressant, and antidepressant alone, found that no difference existed between acupuncture at nonmeridian points and acupuncture at specific treatment points, and that acupuncture plus antidepressant improved depressed symptoms more than antidepressant alone (N = 70).[18]

Recent reviews, which include several studies already presented, assessed 10 randomized controlled trials of acupuncture for depression (N = 671).[19–21] These authors conclude that studies to date provide inconclusive evidence for the benefits of acupuncture for treatment of depression. They detail methodological problems in existing research, as well as the difficulty in interpreting the findings of studies that utilized different types of acupuncture interventions and different control conditions.

Research on the utility of acupuncture for unipolar depression may not translate to the treatment of depressive symptoms in bipolar disorder. There is no controlled research assessing the benefits of acupuncture for any mood symptoms experienced as part of bipolar disorder. In a single case report addressing the use of acupuncture for bipolar disorder, the patient's manic symptoms remitted after 20 acupuncture treatments, and she remained asymptomatic through a 1-year follow-up, although no mention is made of additional pharmacologic interventions.[22]

The current report describes the results of 2 pilot investigations into the safety, acceptability, and effectiveness of acupuncture for symptoms of hypomania and depression in patients with bipolar disorder. The first study was initiated approximately 18 months prior to the second, and the methodology was revised for Study II in response to experiences of Study I. Each study utilized a different type of comparison acupuncture treatment (nonchannel points off meridians or points targeting nonpsychiatric symptoms). These studies provide preliminary data for the acceptability, tolerability, and effectiveness of acupuncture in bipolar populations. They also provide pilot data on the utility of different comparison acupuncture interventions as a viable control in this type of research. We hypothesized that targeted acupuncture would result in greater improvement of mania or hypomania than acupuncture to nonchannel points off meridian, and greater improvement of depression in bipolar patients than acupuncture targeted at somatic, rather than psychiatric, symptoms. A secondary hypothesis was that patients who believed in the effectiveness of acupuncture would have a more positive response.

METHOD

All participants in these studies were volunteers from the community or were recruited from among patients already receiving care from the Bipolar Disorders Research Program at the University of Texas (UT) Southwestern Medical Center. Each trial was approved by the UT Southwestern Medical Center Institutional Review Board. Participants provided written informed consent after receiving verbal and written complete description of the pertinent study. Inclusion criteria were relatively broad, including patients with the full spectrum of bipolar diagnoses, given lack of preliminary data to guide more precise selection.

Study I: Adjunctive Acupuncture for Mood Elevation in Bipolar Disorder

This study (conducted from May 2000 through May 2003) was a 12-week randomized trial assessing the safety, acceptability, and effectiveness of adjunctive

acupuncture for 20 outpatients with bipolar disorder I, bipolar disorder II, or bipolar disorder not otherwise specified who were experiencing symptoms of increased mood lability, hypomania, or mania as evidenced by a Young Mania Rating Scale (YMRS)[23] score greater than 12. Exclusion criteria were limited to those patients with unstable medical illness. Patients, physicians, and independent assessors were blinded to group assignment; however, acupuncturists were informed in order to plan and execute treatment accordingly. One group received targeted acupuncture to points associated with mood elevations (ACU-ME), and the other received off-meridian acupuncture (ACU-OM; needles inserted, but at points off any acupuncture meridian). This latter group received ACU-OM acupuncture for the first 6 weeks and were then crossed over to targeted acupuncture for an additional 6 weeks. The ACU-ME group received treatment for up to 12 weeks. Acupuncture was administered twice per week for the first 3 weeks of the study. After the first 3 weeks of study participation, acupuncture frequency could be dropped to once-per-week if there was an observed decrease in symptom severity.

Study II: Adjunctive Acupuncture for Depression in Bipolar Disorder

This study (conducted from November 2001 through May 2003) assessed the benefits of acupuncture for 30 patients with bipolar disorder I or II experiencing moderate depression as measured by an Inventory of Depressive Symptomatology–Clinician-Rated[24,25] (IDS-C) score greater than or equal to 25. Exclusion criteria included current mixed episode, unstable medical illness, or active substance abuse/dependency. Study entrance required a stable medication regimen for a minimum of 30 days. Patients were randomly assigned to either acupuncture for depression (ACU-D) or a nonpsychiatric acupuncture treatment (ACU-NP). Nonpsychiatric acupuncture involved equal contact with an acupuncturist but targeted body points relevant to other symptom patterns, such as allergies or headaches. As with Study I, patients, research assistants, and physicians administering routine assessment scales were blinded to condition, but acupuncturists were aware so that appropriate treatment could be designed for individual patients. This trial included 12 acupuncture sessions administered over an 8-week period. Those patients who received ACU-NP were offered the option of free sessions of acupuncture for depression after they completed the 8-week trial and were debriefed.

In both studies, bipolar diagnosis was confirmed by Structured Clinical Interview for DSM-IV administered by trained research staff. Acupuncture treatment was added to stable existing medication treatments. In Study I, low-dose, short-term use of lorazepam was available for the management of acute agitation commonly associated with hypomania and mania. Study II required that medications remain stable for a minimum of 30 days prior to randomization into the acupuncture trial. Each study specified mechanisms for termination of study participation in the event of an increase in symptoms, whether depressive or hypomanic. Symptoms, side effects, and satisfaction with treatment were evaluated weekly by a blinded independent assessor, typically a masters-trained full-time employee in our academic research clinic. Participants also had regular visits with study psychiatrists or a psychiatric nurse practitioner to monitor the safety of acupuncture treatments and to assess psychiatric symptoms and potential adverse effects. In each study, acupuncture treatments and visits with the study clinician were provided free of charge. Study II also provided a small monetary compensation at weekly assessment visits to cover costs associated with travel, parking, and time.

Acupuncture Procedures

In both studies, patients received acupuncture treatments in the offices of independent, state-licensed acupuncturists trained in study procedures. In Study I, acupuncturists consulted with an expert (R.S.) to identify points associated with mood elevation, agitation, excess energy, and other features of hypomania or mania. Those receiving nonmeridian acupuncture experienced the same number and duration of needle placements, but to standardized points that are not on any acupuncture meridian. In Study II, acupuncturists were trained in the use of a validated, manualized treatment procedure for major depressive disorder[26] used in several other trials.[13,14,27] Patients completed intake paperwork that allowed the acupuncturist to develop an individualized treatment plan, which included 7 acupuncture points plus 3 ear points. Subjects in the ACU-NP condition experienced similar evaluation and point selection, except the acupuncturist identified another valid symptom pattern, such as allergies or headache, and selected needle points related to that disturbance, rather than the depression. Because of the need to make selections appropriate to each individual, acupuncturists were not blinded to condition in either study. During all acupuncture treatment, needles remained placed for 20 minutes.

Symptom Assessment

Patients completed routine assessments of symptoms and side effects on a weekly basis. These included the IDS-C,[24] Clinical Global Impressions scale for Bipolar Disorder[28] (CGI-BP; includes ratings for depression, mania, and overall symptoms), YMRS[23] (11-item), Global Assessment of Functioning (GAF),[29] and a Side Effects Questionnaire. A self-report instrument assessing patients' beliefs about the effectiveness of acupuncture treatment (Acupuncture Beliefs Scale[30]) was completed at baseline in Study I, and at baseline, week 4, and either week 8 or endpoint in Study II.

Table 1. Baseline Characteristics of Study Participants

Characteristic	Study I (mood elevation) ACU-ME (n = 10)	ACU-OM (n = 10)	p Value[a]	Study II (depression) ACU-D (n = 13)	ACU-NP (n = 13)	p Value[a]
Men, % (n)	50.0 (5)	40.0 (4)	> .99	7.7 (1)	53.8 (7)	.03
Age, mean (SD), y	39.2 (11.5)	35.3 (9.2)	.41	39.7 (10.5)	42.8 (9.1)	.42
White, % (n)	60.0 (6)	90.0 (9)	.30	84.6 (11)	100.0 (13)	.48
Bipolar I disorder, % (n)	60.0 (6)	60.0 (6)	> .99	46.2 (6)	30.8 (4)	.69
Age at onset of mood symptoms, mean (SD), y	19.9 (8.8)	16.0 (9.4)	.39	16.8 (9.1)	15.2 (6.5)	.59
No. of depressive episodes in previous year, mean (SD)	2.3 (1.4)	2.9 (3.0)	.61	2.1 (2.1)	3.2 (2.8)	.27
No. of manic/hypomanic episodes in previous year, mean (SD)	1.7 (0.7)	2.3 (1.0)	.16	3.0 (4.1)	1.8 (2.1)	.40
Baseline YMRS score, mean (SD)	20.9 (5.8)	19.2 (7.3)	.58	5.1 (3.4)	4.0 (3.0)	.42
Baseline IDS-C score, mean (SD)	21.7 (11.0)	24.4 (7.1)	.52	32.2 (9.8)	33.0 (7.9)	.83
Acupuncture Beliefs Scale score, mean (SD)	135.4 (15.9)	147.1 (14.9)	.13	138.9 (14.5)	134.0 (17.9)	.48

[a]For categorical parameters, Fisher exact test is used. For continuous parameters, a 2-sample t test is performed.
Abbreviations: ACU-D = acupuncture for depression group, ACU-ME = acupuncture for mood elevation group, ACU-NP = acupuncture for nonpsychiatric symptoms group, ACU-OM = acupuncture–off meridian group, IDS-C = Inventory for Depressive Symptomatology–Clinician-Rated, YMRS = Young Mania Rating Scale.

Statistical Analysis

The specific and comparison acupuncture groups in both studies were compared for baseline characteristics (sex, age, race, bipolar diagnosis, age at onset of bipolar symptoms, and number of depressive and hypomanic/manic episodes in the previous year) using a 2-sample t test for continuous measures (e.g., age) and Fisher exact tests for categorical measures (e.g., gender).

A random regression model repeated-measures analysis of variance[31] was performed for each outcome measure (IDS-C, YMRS, GAF, and CGI-depression, CGI-mania, and CGI-overall). The model consisted of the independent variables group (acupuncture or comparison), time (weeks), and the group-by-time interaction. A significant group-by-time interaction indicated a difference between groups across time. All analyses were performed using the SAS statistical software (SAS Institute, Inc., Cary, North Carolina) using a significance level of 0.05.

RESULTS

Study I: Adjunctive Acupuncture for Mood Elevation in Bipolar Disorder

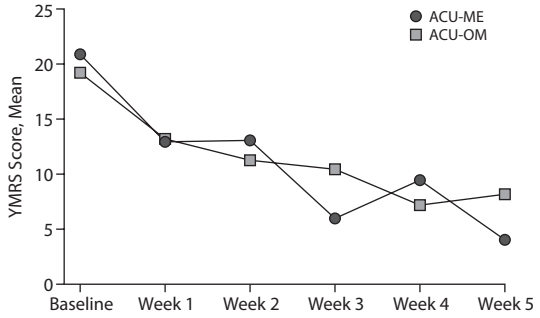
Twenty patients were randomly assigned to either the targeted acupuncture for mood elevation (ACU-ME; n = 10) or off-meridian acupuncture (ACU-OM; n = 10). At baseline, all patients exhibited moderate levels of hypomania, with mean YMRS scores at randomization of 20.9 ± 5.8 for ACU-ME and 19.2 ± 7.3 for ACU-OM. There were no baseline demographic differences between the groups (Table 1). Of the 20 patients randomly assigned, 10 (50%) completed the 12-week study. From each group, 5 patients discontinued early. In the ACU-ME group, 3 patients were noncompliant with the protocol and 2 had worsening mood into depression. In the ACU-OM group, 2 patients had worsening mood (1 into worsening hypomania, 1 into depression), 2 patients were lost to follow-up, and 1 patient was noncompliant with the protocol. Overall, there was no difference between groups in time in the trial (mean [SD] days in trial for the ACU-ME group equal 48.70 [31.80]; ACU-OM = 57.30 [31.50]; not significant). In general, those who discontinued did so early in study participation, with 8 of the 10 dropping out before week 5. Additionally, the timing of the switch to active acupuncture for patients in the ACU-OM group and coordination of acupuncture and assessment visits was potentially confusing, and we believe that some patients were switched prematurely. For these reasons, analyses in this study were restricted to the first 5 weeks of active treatment, the time for which we are most confident in our direct comparison of ACU-ME and ACU-OM for acute hypomania.

Primary and secondary outcomes over the first 5 weeks of treatment were essentially equivalent across groups. Each group experienced an overall decline in manic symptoms and improvement in functioning, and there was no evidence for any group differences over time. Specifically, all of the group differences and group × visit interactions had p values > .05. The visit slopes for the YMRS and the CGI-mania were significant beyond the .001 level; the visit slopes for the IDS-C, GAF, CGI-depression, and CGI-overall were nonsignificant (p > .05), although the CGI-overall did trend toward significance (p = .10). Estimated mean ± SD endpoint YMRS scores were 1.58 ± 2.89 for the ACU-ME group and 10.01 ± 2.47 for the ACU-OM group. Figure 1 illustrates mean estimated YMRS scores over the first 5 weeks of treatment for the 2 groups (for actual scores, see Table 2). As can be seen, both groups improved to an equal extent.

There was no statistical difference between the 2 treatment groups at baseline in scores on the Acupuncture Belief Questionnaire. The correlation between acupuncture beliefs and YMRS baseline-exit change (r = –0.80) was significant (p = .02).

In both groups, the majority of patients received stable doses of psychiatric medications. The most common

Figure 1. Mean Estimated Young Mania Rating Scale (YMRS) Scores by Group Over Time: Study I



Abbreviations: ACU-ME = acupuncture for mood elevation, ACU-OM = acupuncture–off meridian.

medications received across groups were valproic acid (n = 8) and lithium (n = 6). Table 3 illustrates the types and number of concomitant medications taken by patients in each group.

Side effects, which were rated possibly, probably, or definitely related to treatment, were reported by 56% of patients in the ACU-ME group (n = 5; only 9 persons in this group completed at least 1 side effect rating scale) and by 60% of patients (n = 6) in the ACU-OM group. Side effects reported by 2 patients in the ACU-ME group were increased appetite, tiredness, increased sexual interest, increased weight, and ringing in ears. Side effects reported by 3 patients in the ACU-OM group were increased appetite and increased thirst, and those reported by 2 patients in the ACU-OM group were dry mouth, itching, increased urinary frequency, increased sexual interest, and drowsiness/sedation. Only 3 patients complained of side effects directly related to the acupuncture experience. These included soreness, bruising, and bleeding at site of needle insertion. The mean number of side effects reported by the ACU-ME group was 3.3 and for the ACU-OM group was 2.2 (p = .44).

Study II: Adjunctive Acupuncture for Depression in Bipolar Disorder

Of the 30 patients who signed informed consent forms and completed baseline measures, 26 patients were randomly assigned to either a specific acupuncture for depression (n = 13) (ACU-D) or nonspecific acupuncture for nonpsychiatric conditions (n = 13) (ACU-NP) group. Participants in this study demonstrated moderate to severe levels of depression, with mean ± SD IDS-C scores at randomization of 32.2 ± 9.8 for ACU-D and 33.0 ± 7.9 for ACU-NP. The 2 groups were similar demographically except that there were more women in the ACU-D group (men, n = 1) than in the control group (ACU-NP; men, n = 7) (see Table 1, $p < .05$). Of the 26 patients randomly assigned, 19 (73%) completed the 8-week active

Table 2. Summary Statistics for Primary Outcomes Over Time

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
Group	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n
STUDY I: YMRS Scores																		
ACU-ME	20.9 ± 5.8	10	12.8 ± 7.4	9	13.1 ± 6.1	8	5.9 ± 5.2	8	9.5 ± 9.6	6	4.0 ± 4.1	5						
ACU-OM	19.2 ± 7.3[a]	10	13.2 ± 7.1	10	11.2 ± 5.7	8	10.4 ± 8.8	6	7.1 ± 3.9	6	8.2 ± 6.6	7						
STUDY II: IDS-C Scores																		
ACU-D	32.2 ± 9.8[a]	13	26.8 ± 9.2	13	22.1 ± 12.3	12	17.5 ± 7.3	11	18.7 ± 10.0	10	19.0 ± 11.6	9	16.2 ± 12.0	9	18.3 ± 14.7	9	16.7 ± 15.8	9
ACU-NP	33.0 ± 7.9	13	23.8 ± 9.2	13	20.9 ± 8.9	13	21.0 ± 9.6	11	19.6 ± 11.3	11	17.8 ± 10.2	10	17.5 ± 9.0	10	15.0 ± 7.8	10	18.1 ± 10.8	10

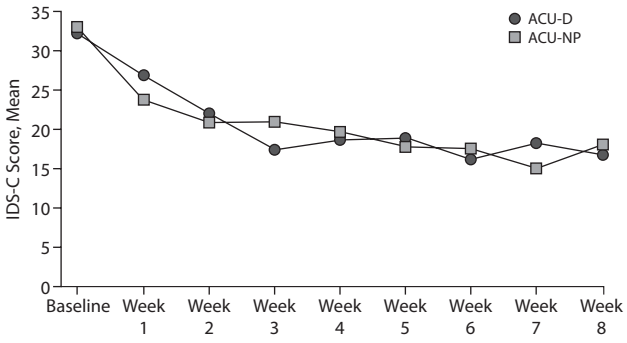
[a]95% confidence interval: lower limit, upper limit.
Abbreviations: ACU-D = acupuncture for depression group, ACU-ME = acupuncture for mood elevation group, ACU-NP = acupuncture for nonpsychiatric symptoms group, ACU-OM = acupuncture–off meridian group, IDS-C = Inventory for Depressive Symptomatology–Clinician-Rated, YMRS = Young Mania Rating Scale.

Table 3. Concomitant Medications

	Study I		Study II	
Medication	ACU-ME	ACU-OM	ACU-D	ACU-NP
Type of medication				
Lithium	2	4	2	2
Anticonvulsants				
Valproic acid	3	5	3	3
Carbamazepine	1	0	2	0
Gabapentin	2	0	1	0
Oxcarbazepine	1	2	3	1
Topiramate	2	1	1	2
Lamotrigine	2	0	0	0
Antidepressants[a]				
Bupropion	2	2	4	4
Citalopram	0	1	1	2
Fluoxetine	4	0	0	2
Mirtazapine	0	0	1	0
Paroxetine	0	0	2	1
Sertraline	0	0	2	1
Trazodone[b]	2	0	0	2
Venlafaxine	0	0	0	3
Atypical antipsychotics				
Clozapine	0	0	0	1
Olanzapine	0	0	1	0
Quetiapine[b]	1	1	3	2
Benzodiazepine				
Alprazolam	0	1	1	0
Clonazepam	1	3	0	3
Diazepam	0	0	3	0
Lorazepam	0	0	1	0
Typical antipsychotics				
Perphenazine	0	0	0	1
Thiothixene	0	0	1	0
Zolpidem	0	1	2	2
Antihistamine for sleep	0	0	1	3
Melatonin	0	0	1	0
No. of medications				
0	1	1	0	0
1	1	4	4	4
2	2	2	1	2
3	4	1	3	2
4	1	0	4	4
5	0	1	1	1
6	0	1	0	0

[a]One patient in the ACU-ME group received 2 antidepressants, fluoxetine and trazodone.
[b]These medications were prescribed for sleep: quetiapine at 25 mg/day, trazodone at 50–100 mg/day.
Abbreviations: ACU-D = acupuncture for depression, ACU-ME = acupuncture for mood elevation, ACU-NP = acupuncture for nonpsychiatric symptoms, ACU-OM = acupuncture–off meridian.

Figure 2. Mean Estimated Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C) Scores by Group Over Time: Study II



Abbreviations: ACU-D = acupuncture for depression, ACU-NP = acupuncture for nonpsychiatric symptoms.

treatment phase of the study. Of those who withdrew before completion of the trial, 4 were withdrawn due to worsening symptoms (2 from each group), 2 were lost to follow-up (1 from each group), and 1 patient was withdrawn for "unknown" reasons (from the ACU-D group). There was no difference between groups in number of days of study participation. Those in the ACU-D group completed a mean of 45.46 days (SD = 18.84 days), and those in the ACU-NP group completed a mean of 48.85 days (SD = 16.07 days).

Both groups showed improvement over time on the IDS-C, the GAF, the CGI-depression, and the CGI-overall scales ($p < .001$). Mean ± SD baseline IDS-C scores were 32.2 ± 9.8 for the ACU-D group and 33.0 ± 7.9 for the ACU-NP group. Estimated mean ± SD IDS-C exit scores were 16.9 ± 2.9 for the ACU-D group and 17.6 ± 2.8 for the ACU-NP group. Neither group showed improvement over visits on the YMRS or CGI-mania scales ($p > .05$). Both groups experienced an overall reduction in symptoms and improvement in functioning, with no evidence of a group effect over time ($p > .05$). Figure 2 contains the mean estimated IDS-C total scores, by visit, for the 2 groups (for actual scores, see Table 2). As can be seen, both groups improved to an equal extent.

Scores on the Acupuncture Belief Scale were significantly correlated with baseline-exit change on the IDS-C ($r = 0.49$; $p = .03$).

Five patients in the ACU-D group (38%) and 9 patients (69%) in the ACU-NP group reported side effects that were evaluated to be possibly, probably, or definitely related to treatment. Side effects experienced by at least 2 patients in the ACU-D group were headache, increased sweating, increased appetite, increased thirst, ataxia, tiredness, constipation, diarrhea, nausea, upset stomach, dizziness/lightheadedness, blurred vision, decreased sexual interest, insomnia, excessive sleeping, increased weight, ringing in ears, and impaired memory. Side effects experienced by at least 2 patients in the ACU-NP group were dry mouth, increased thirst, tiredness, diarrhea, feeling dull, increased appetite, change in the way things taste, stiffness, headache, nausea, increased sexual interest, drowsiness/sedation, and cognitive slowing. Two patients reported adverse effects directly associated with the acupuncture experience (finger pain and soreness/bleeding at the site of needle insertion). Patients in the ACU-D group experienced a mean of 1.2 unique side effects each; patients in the ACU-NP group reported a mean of 1.1 unique side effects over the duration of the study ($p = .83$).

DISCUSSION

The current report includes findings from 2 randomized controlled pilot trials assessing the effectiveness of adjunctive acupuncture for mood symptoms associated with bipolar disorder. They represent the first randomized trials of acupuncture for the treatment of either mood elevation or depression in patients with bipolar disorders. Study psychiatrists, patients, and research staff completing assessment measures were blind to group assignment. In order to provide individualized, targeted treatment, acupuncturists were not blind to group assignment.

Both studies provide partial support for the acceptability of acupuncture as an adjunctive treatment for patients with bipolar disorders. Our initial expectation on initiating these studies was that interest would be high, in part based on preliminary surveys[6] and national data. To our surprise, recruitment was slower than usual, leading to prolonged enrollment times, and persisting despite advertisement in holistic newspapers and grocery stores specializing in organic produce. Difficulties in recruitment may be due, in part, to the chronicity and severity of bipolar disorder and patient education efforts that have emphasized the need for pharmacologic management of symptoms of this disorder. Additionally, there are many preconceptions about acupuncture, including the thought that needling procedures are painful and frightening, which may have reduced interest. It is possible that those patients who eventually volunteered and were randomly assigned might be somewhat different from the average patient with bipolar disorder in their openness and willingness to try alternative approaches to treat bipolar symptoms.

Once enrolled, however, there was no difference in time in treatment across conditions, suggesting that acceptability of specific acupuncture and the control conditions was similar for those participants who were willing to attempt the intervention. Patients also reported positive and, in many cases, enthusiastic reports of their acupuncture experiences, regardless of group membership. There were very few adverse effects directly associated with acupuncture, and no dropout associated with adverse effects in either trial. While attrition was high in the mood elevation study (50% did not complete the trial), the mean baseline YMRS scores for this group were also high. As treating psychiatrists had discretion for removing patients with escalating symptoms from the trial, the threshold for withholding more aggressive interventions to curtail escalation into a full manic episode was likely low. Alternatively, the initial visit schedule (2 acupuncture sessions plus an assessment in the first week) may have been too rigorous for patients experiencing hypomanic and manic symptoms. In the depression study, 73% completed the 8-week trial.

The studies also provide preliminary data on the effectiveness of adjunctive acupuncture for symptoms of bipolar disorder. While neither study found a significant difference between acupuncture and control conditions, which included off-meridian acupuncture (Study I) and nonpsychiatric acupuncture (Study II), patients in all groups improved during study participation. In Study II, all patients moved from moderate depression symptom scores to scores indicative of mild depression over the 8-week trial. Results from Study I are more difficult to interpret, as there was considerable attrition in the early weeks (likely due to patients continuing to have symptoms that interfered with their ability to comply with the trial or that required more aggressive intervention). While mean YMRS scores were reduced below clinical thresholds for those that remained in the pilot, there was a lot of individual variability in patient response.

It is possible that the overall improvement, regardless of type of acupuncture received, is due to control conditions providing active benefit to study patients. There is currently no agreed upon placebo replacing active acupuncture treatment.[32] Other authors have noted the challenge in choosing control conditions, as trials in major depressive disorder have provided inconsistent evidence that genuine acupuncture is superior to placebo acupuncture conditions.[19] In the hypomania study (launched first), we chose acupuncture to points off the meridian as a control condition. This ensures that patients have similar needling experiences, but the procedure is believed to have no benefit. Due to growing concerns about providing an inert, but invasive procedure, we chose nonpsychiatric acupuncture as a control condition for the depression study. In this condition, patients received acupuncture that was appropriate to relieve a nonpsychiatric concern (for example, allergies or headache), but that wasn't believed to be helpful in treating depression. In both control conditions, patients are exposed to a needling procedure in a similar environment and duration to specific or targeted acupuncture. The choice of control conditions represents 2 efforts to design randomized acupuncture trials that are scientifically rigorous yet ethically acceptable, but may have reduced our potential to find group differences. In the case of acupuncture to points off the acupuncture meridians, these points may be close enough to specific points to trigger a positive response.[33] It is also possible that acupuncture that targets somatic, rather than psychiatric, complaints may also improve depression, as depression can have a significant somatic component.[34]

Other possible explanations for the similar symptom reduction observed in specific acupuncture versus control conditions is the possibility that the acupuncture procedure itself, which is often described as relaxing, and the expectations for symptom relief may help produce the symptom reductions observed in both control conditions. There was a positive association between scores on the

Acupuncture Beliefs Scale and symptom reduction in the depression study, suggesting that strong beliefs in the potential benefit of acupuncture were associated with greater symptom reduction. The negative association between scores on the Acupuncture Beliefs Scale and symptom reduction in the hypomania study is surprising, and may be an artifact of the small sample size or possibly a symptom of the hypomania itself—patients experiencing high levels of hypomania may have had a more positive attitude toward acupuncture, but may also have discontinued early due to inability to comply with study procedures or concern about elevated mood. Additionally, all study patients had regular interaction with and attention from research coordinators, psychiatrists, and study acupuncturists, and this increased attention may have been beneficial.

Importantly, in both trials, patients treated with adjunctive acupuncture or control conditions experienced decreases in the respective symptom of interest, i.e., mood elevation or depression. In Study I, treating hypomanic and manic symptoms, YMRS scores decreased an average of 11.6 points while IDS-C scores, measuring depression, decreased by an average of 1 point. Those patients in the control condition (ACU-OM) experienced reductions in depression symptom ratings of 7 points (about 25%; IDS-C score). In Study II, which treated depression in patients with bipolar disorders, IDS-C scores dropped an average of 13.2 points or almost 50% for those receiving active acupuncture for depression, while YMRS scores decreased by an average of only 1.6 points. While those patients in control conditions also improved, their improvement was less specific to the pole of interest and reflected a more general improvement in both poles over time. These outcomes would be considered very positive results in most trials assessing medication treatments, and represent clinically meaningful decreases in symptoms.

Overall, these 2 pilot studies provide illustration of the difficulty of conducting scientifically rigorous studies of acupuncture. However, they do suggest that for those patients who are interested and open to trying adjunctive acupuncture, treatment can be beneficial. Given the limitations of the trial for mood elevation (only 4 individuals completed the initial 6-week acute phase in active treatment), further work is needed to determine whether acupuncture is helpful in treatment of this pole of bipolar illness. However, there is no evidence that adjunctive acupuncture, in the presence of continued pharmacologic management, is harmful to these patients. For patients with moderate depression, a regular routine of acupuncture was helpful in reducing symptoms to mild levels. Side effects were limited, and there is preliminary evidence that acupuncture treatment may be focused to treat different poles of bipolar symptoms. Larger controlled trials will be needed to further study the benefits of acupuncture for treatment of bipolar disorder. These should include comparison of multiple appropriate control conditions and further definition of specific patient characteristics (i.e., direction and/or intensity of mood symptoms, diagnostic subgroup) best suited for this adjunctive treatment.

Drug names: alprazolam (Xanax, Niravam, and others), bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), diazepam (Diastat, Valium, and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), norepinephrine (Levophed and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), sertraline (Zoloft and others), thiothixene (Navane and others), topiramate (Topamax), valproate (Depacon and others), valproic acid (Stavzor, Depakene, and others), venlafaxine (Effexor and others), zolpidem (Zolpimist, Ambien, and others).

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