Annals of Internal Medicine | ARTICLE

Effectiveness of Acupuncture as Adjunctive Therapy in Osteoarthritis of the Knee

A Randomized, Controlled Trial

Brian M. Berman, MD; Lixing Lao, PhD; Patricia Langenberg, PhD; Wen Lin Lee, PhD; Adele M.K. Gilpin, PhD; and Marc C. Hochberg, MD

Background: **Evidence on the efficacy of acupuncture for reducing the pain and dysfunction of osteoarthritis is equivocal.**

Objective: **To determine whether acupuncture provides greater pain relief and improved function compared with sham acupuncture or education in patients with osteoarthritis of the knee.**

Design: **Randomized, controlled trial.**

Setting: **Two outpatient clinics (an integrative medicine facility and a rheumatology facility) located in academic teaching hospitals and 1 clinical trials facility.**

Patients: **570 patients with osteoarthritis of the knee (mean age [±SD], 65.5 ± 8.4 years).**

Intervention: **23 true acupuncture sessions over 26 weeks. Controls received 6 two-hour sessions over 12 weeks or 23 sham acupuncture sessions over 26 weeks.**

Measurements: **Primary outcomes were changes in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores at 8 and 26 weeks. Secondary outcomes were patient global assessment, 6-minute walk distance, and physical health scores of the 36-Item Short-Form Health Survey (SF-36).**

Results: **Participants in the true acupuncture group experienced greater improvement in WOMAC function scores than the sham acupuncture group at 8 weeks (mean difference, −2.9 [95% CI, −5.0 to −0.8]; $P = 0.01$) but not in WOMAC pain score (mean difference, −0.5 [CI, −1.2 to 0.2]; $P = 0.18$) or the patient global assessment (mean difference, 0.16 [CI, −0.02 to 0.34]; $P > 0.2$). At 26 weeks, the true acupuncture group experienced significantly greater improvement than the sham group in the WOMAC function score (mean difference, −2.5 [CI, −4.7 to −0.4]; $P = 0.01$), WOMAC pain score (mean difference, −0.87 [CI, −1.58 to −0.16]; $P = 0.003$), and patient global assessment (mean difference, 0.26 [CI, 0.07 to 0.45]; $P = 0.02$).**

Limitations: **At 26 weeks, 43% of the participants in the education group and 25% in each of the true and sham acupuncture groups were not available for analysis.**

Conclusions: **Acupuncture seems to provide improvement in function and pain relief as an adjunctive therapy for osteoarthritis of the knee when compared with credible sham acupuncture and education control groups.**

Ann Intern Med. 2004;141:901-910. **www.annals.org**

For author affiliations, see end of text.

See related articles on pp 911-919 and pp 920-928.

Osteoarthritis is the most common form of arthritis and is a major cause of morbidity, limitation of activity, and health care utilization, especially in elderly patients (1, 2). Pain and functional limitation are the primary clinical manifestations of osteoarthritis of the knee. Current recommendations for managing osteoarthritis, including guidelines published by the American College of Rheumatology (3) and European League of Associations of Rheumatology (4), focus on relieving pain and stiffness and maintaining or improving physical function as important goals of therapy. No curative therapies exist for osteoarthritis; thus, both pharmacologic and nonpharmacologic management focus on controlling pain and reducing functional limitation (5). Nonpharmacologic therapy, which includes patient education, social support, physical and occupational therapy, aerobic and resistive exercises, and weight loss, is the cornerstone of a multidisciplinary approach to osteoarthritis patient management (3). Pharmacologic therapies include nonopioid analgesics (such as acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs) (including cyclooxygenase-2 [COX-2] enzyme selective inhibitors), topical analgesics (capsaicin cream), opioid analgesics, and intra-articular steroid and hyaluronate injections. Often, these agents are used in combination for additive analgesic efficacy (6). Pharmacologic management of osteoarthritis is often ineffective, and agents such as NSAIDs may cause unwanted and dangerous side effects (7, 8).

Complementary and alternative medicine is another approach to treating osteoarthritis (9–12), particularly in Asian societies (13). Many U.S. patients with osteoarthritis also use complementary and alternative medical therapies (14).

A systematic review of acupuncture and knee osteoarthritis (15) identified 7 small randomized, controlled trials published in English. Within the methodologic limitations of the studies, the evidence suggested that acupuncture seemed to alleviate knee pain and function compared with "sham" acupuncture controls, although 2 trials comparing acupuncture with an active, nonpharmacologic treatment (physical therapy) did not indicate such an effect (16, 17).

Before conducting our large-scale trial, we completed both a pilot study (18) and a randomized, single-blind trial (19) of the effect of acupuncture on osteoarthritis of the knee. Participants in the uncontrolled pilot study ($n = 12$) showed statistically significant improvement in both self-reported pain and physical function, as well as performance measures of physical function after 8 weeks of acupuncture treatment and at 12-week follow-up as compared with their baseline (18). In our larger randomized, single-blind

Context

Previous studies of acupuncture for osteoarthritis have had conflicting results. This may have occurred because most studies have included small samples, a limited number of treatment sessions, or other limitations.

Contribution

This randomized, controlled trial compared 24 acupuncture sessions over 26 weeks with sham acupuncture or arthritis education in 570 patients with osteoarthritis of the knee. Acupuncture led to greater improvements in function but not pain after 8 weeks and in both pain and function after 26 weeks. No adverse effects were associated with acupuncture.

Cautions

Many participants dropped out of the study, so readers should interpret the findings at 26 weeks with caution.

–The Editors

trial ($n = 73$), which examined the benefit of acupuncture added to standard management with NSAIDs, the acupuncture treatment group experienced statistically significant improvements in self-reported pain and disability scores compared with a standard-care control group as late as 4 weeks after the end of treatment (19). However, this effect diminished within 18 weeks (26 weeks after the beginning of the trial) after the final acupuncture treatment.

Together, however, the previously conducted trials (both our preliminary studies [18, 19] and those referenced in the systematic review [15]) have 3 methodologic limitations: lack of credible controls for the placebo effect, inadequate assessment of long-term treatment benefits, and insufficient sample sizes.

We tested the hypothesis that an 8-week intensive acupuncture treatment regimen, followed by an 18-week tapering regimen, reduces pain and improves function among patients with knee osteoarthritis as compared with both sham acupuncture and education control groups.

METHODS

Patient Recruitment

We recruited patients for this multisite, placebo-controlled trial from March 2000 through December 2003, primarily through print and radio advertisements. The 3 sites were the Integrative Medicine Clinic of the University of Maryland School of Medicine, Baltimore, Maryland; the Innovative Medical Research Center (a private research firm), Towson, Maryland; and the Hospital for Special Surgery, New York City, New York. The institutional review boards of the 3 sites approved the study.

We determined the sample size ($n = 570$) by a power analysis based on our randomized pilot study (19), adjusted by the estimated decrease in effect size resulting from the inclusion of a sham acupuncture group designed to control for placebo effects.

Patients met the following inclusion criteria: age 50 years or older, a diagnosis of osteoarthritis of the knee, radiographic evidence of at least 1 osteophyte at the tibiofemoral joint (Kellgren–Lawrence grade ≥ 2), moderate or greater clinically significant knee pain on most days during the past month, and willingness to be randomly assigned. Exclusion criteria were the presence of serious medical conditions that precluded participation in study, bleeding disorders that might contraindicate acupuncture, intra-articular corticosteroid or hyaluronate injections (as well as any knee surgeries or concomitant use of topical capsaicin cream) during the past 6 months, previous experience with acupuncture, or any planned events (including total knee replacement) that would interfere with participation in the study during the following 26 weeks.

After a brief telephone screening, patients were scheduled to visit 1 of the 3 participating sites to sign an informed consent statement and undergo a brief rheumatologic examination (including radiographic examination of affected knees) by a physician or a nurse practitioner. Because the education course was a group activity, patients were recruited until a cohort of 12 to 21 patients was formed, at which point each cohort at each site was randomly assigned to 1 of 3 groups by a computer-generated process using randomly selected blocks of 3, 6, and 9. We assured allocation concealment by using disguised letter codes that were generated and sent to the site coordinators by a central statistical core. We used this procedure to ensure that approximately equal numbers of participants were in each treatment group across the course of the study, to ensure that each cohort would have participants assigned to all 3 treatment groups, and to make the breaking of the group assignment process more difficult. The research assistants who collected assessments from participants, the participants themselves (in the true acupuncture and sham acupuncture groups), and the statistician were blinded to group assignment. Assessments were conducted at baseline and 4, 8, 14, and 26 weeks after randomization.

Study Interventions

We developed and modified the acupuncture treatment and sham control protocols from previously reported and validated procedures (18–21). During the trial, 7 acupuncturists were used: 3 at the Integrative Medicine Clinic, 3 at the Innovative Medical Research Center, and 1 at the Hospital for Special Surgery. In general, acupuncturists were assigned to the same participants throughout the 26-week treatment schedule, except for vacation conflicts and staff turnover, and provided approximately the same proportions of true versus sham procedures. All acupuncturists were state-licensed and had at least 2 years of clinical experience. The study's principal acupuncturist trained and supervised the acupuncturists in performing true or sham

procedures and avoiding interactions that could inadvertently communicate group assignment.

True Acupuncture

The true acupuncture (experimental) group underwent 26 weeks of gradually tapering treatment according to the following schedule: 8 weeks of 2 treatments per week followed by 2 weeks of 1 treatment per week, 4 weeks of 1 treatment every other week, and 12 weeks of 1 treatment per month. We based the acupuncture point selections on Traditional Chinese Medicine meridian theory to treat knee joint pain, known as the "Bi" syndrome. These points consisted of 5 local points (Yanglinquan [gall bladder meridian point 34], Yinlinquan [spleen meridian point 9], Zhusanli [stomach meridian point 36], Dubi [stomach meridian point 35], and extra point Xiyan) and 4 distal points (Kunlun [urinary–bladder, meridian point 60], Xuanzhong [gall bladder meridian point 39], Sanyinjiao [spleen meridian point 6], and Taixi [kidney meridian point 3]) on meridians that traverse the area of pain (22, 23). The same points were treated for each affected leg. If both knees were affected, 9 needles were inserted in each leg. (The outcome measures were not specifically targeted to whether the patient had osteoarthritis in 1 or both knees, and we observed no differential effects on the basis of the number of knees treated.) The acupuncturists inserted 1.5-inch (for local points) and 1-inch (for distal points) 32-gauge (0.25-mm diameter) acupuncture needles to a conventional depth of approximately 0.3 to 1.0 inch, depending on point location. All participants in the treatment group achieved the "De-Qi" sensation, a local sensation of heaviness, numbness, soreness, or paresthesia that accompanies the insertion and manipulation of needles during acupuncture, at these 9 points. Acupuncturists applied electrical stimulation (Micro-850, Texas Medical, Waxahachie, Texas) at knee points Xiyan, at low frequency (8 Hz), and square biphasic pulses (0.5-ms pulse width) for 20 minutes. We chose this single location because of its theoretical importance, the impracticality of applying electrical stimulation to as many as 9 points in a clinical trial, and our desire to use the same procedure that we had piloted in our previously successful trial.

To ensure that the procedures in the treatment and control groups were as similar as possible, we tapped 2 guiding tubes at 2 sham points in the abdominal area, approximately 3 cm lateral to and slightly above the umbilicus bilaterally, and immediately affixed a pair of needles to the surface of the same points, without needle insertion, with adhesive tape. We chose this site for 2 reasons. First, the site was between 2 meridians that are theoretically irrelevant to knee pain. Second, we wanted the participants in both groups to have the opportunity to feel actual needle insertion to facilitate blinding.

Sham Control

For the sham treatment, we modified a combined insertion and noninsertion procedure from our previously validated placebo acupuncture method (20, 21). Acupuncturists inserted 2 needles into the sham points in the abdominal area, approximately 3 cm lateral to and slightly above the umbilicus bilaterally, and then immediately applied 2 pieces of adhesive tape next to the needles. In addition, they tapped a mock plastic needle guiding tube on the surface of each of the 9 true points in the leg to produce some discernible sensation and then immediately applied a needle with a piece of adhesive tape to the dermal surface, without needle insertion, of each point for a total of 20 minutes (21). The sham acupuncture procedure was given on the same schedule as the experimental group and used the same active needle placements, except actual insertion did not occur at these 9 points. Although electrical stimulation did not occur, a mock transelectrical stimulation unit (which emitted a sound and possessed a blinking light) was attached to the sham needles at the knee. To facilitate blinding, we used screens in both treatment and sham groups that were placed below the abdomen to prevent participants from actually observing the true or sham procedures at the knee area but to allow them to observe the procedure being performed in the abdomen area.

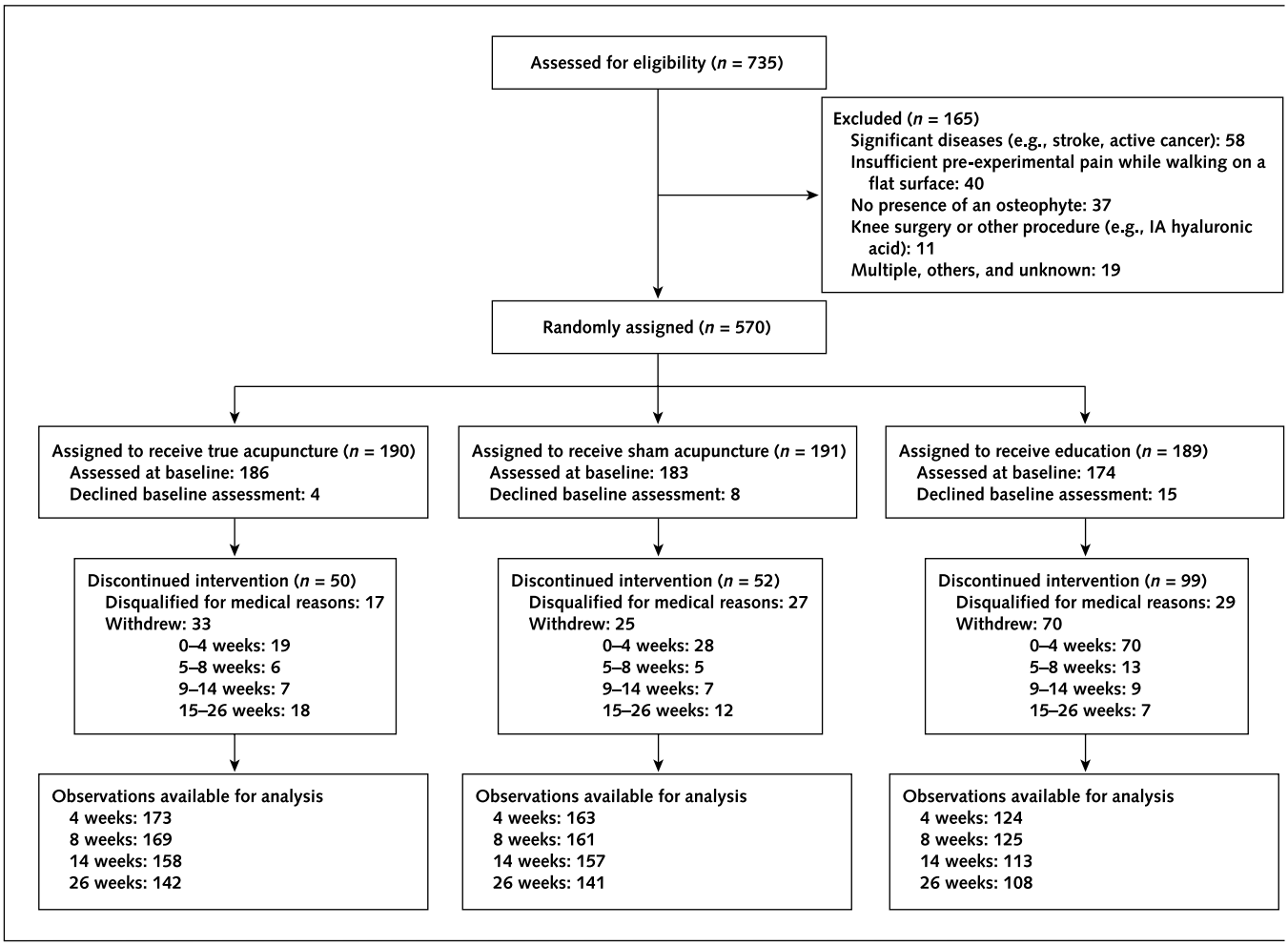
Education Control

The education–attention control consisted of 6 two-hour group sessions based on the Arthritis Self-Management Program (24) and taught by an experienced, Arthritis Foundation–trained patient education specialist. In addition, we periodically mailed educational materials to the education group in an attempt to equalize the amount of experimental contact in all groups.

Outcome Measures

The primary outcome variables for the study, specified a priori, were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores (25). The time point at which we expected to observe the largest experimental effect was 8 weeks, although we were equally interested in the 26-week assessment to ascertain whether these effects could be maintained by our tapered treatment protocol. Secondary outcomes were the 36-Item Short-Form Health Survey (SF-36) physical component score (26), the patient global assessment (27), and the 6-minute walk time (which measured how many feet a patient could walk comfortably on a flat surface in 6 minutes). In addition to baseline, we assessed participants at 4, 8, 14, and 26 weeks on the 2 WOMAC scales and patient global assessment measures and at 8 and 26 weeks on the SF-36 and 6-minute walk outcomes. We assessed patients' self-reports of adverse events potentially related to acupuncture at each measurement interval by using a previously developed questionnaire (19, 21). We asked participants in the true and sham acupuncture groups to report

Figure. **Participant flowchart.**



which treatment they believed they were receiving at 4 and 26 weeks.

Statistical Analysis

Initial analyses tabulated demographic and baseline characteristics of the study participants by randomization group, and we used chi-square tests and 1-way analyses of variance to compare the 3 groups on these characteristics.

Longitudinal analyses examined mean change from baseline at 4, 8, 14, and 26 weeks by using a mixed-model approach as implemented by the MIXED procedure in SAS, version 8.2 (SAS Institute, Inc., Cary, North Carolina). The within-patient correlation structure was best fit by a Toeplitz (banded) covariance matrix with clinical site controlled by its inclusion as a random effect, although the site effect was small. We included the baseline value of the outcome variable as a covariate in all analyses of change from baseline to assess whether change differed by baseline level.

Since mixed-model analysis assumes that data missing at later time points are missing at random, we compared (within treatment group) baseline characteristics of those who were lost to follow-up during the study with characteristics of those whose data were obtained. For patients lost to follow-up by 8 weeks, we found no statistically significant differences within group by race, education, number of affected knees, 1-month history of pain before baseline, or either the WOMAC pain or function scales at baseline. For patients who dropped out by 26 weeks, we found no differences in baseline characteristics except for pain, with dropouts from the education control ($P = 0.05$) and true acupuncture ($P = 0.04$) groups reporting statistically significantly more pain at baseline than participants who completed the study. Furthermore, as indicated in the **Figure**, attrition was higher at 8, 14, and 26 weeks in the education control than the 2 acupuncture groups. (The proportion of dropouts between true and sham acupuncture groups did not differ.)

To further examine the effects of this loss to follow-up, we performed a multiple imputation analysis as implemented by the MI and the MIANALYZE procedures in

Table 1. **Participant Demographic and Baseline Characteristics***

Characteristic	True Acupuncture (*n* = 190)	Sham Acupuncture (*n* = 191)	Education Control (*n* = 189)	Total† (*n* = 570)
Age, *y*	65.2 ± 8.4	66.2 ± 8.7	65.1 ± 8.8	65.5 ± 8.6
Sex, *n (%)*				
Women	120 (63.2)	118 (61.8)	127 (67.2)	365 (64.0)
Men	70 (36.8)	73 (38.2)	62 (32.8)	205 (36.0)
Education, *n (%)*				
No college	62 (32.8)	48 (25.4)	66 (35.1)	176 (31.1)
Some college	127 (67.2)	141 (74.6)	122 (64.9)	390 (68.9)
Race, *n (%)*				
White	133 (70.0)	135 (70.7)	126 (66.7)	394 (69.1)
African American	52 (27.4)	51 (26.7)	60 (31.7)	163 (28.6)
Other	5 (2.6)	5 (2.6)	3 (1.6)	13 (2.3)
Target knees, *n (%)*				
1 knee	141 (75.0)	135 (71.1)	146 (78.1)	422 (74.7)
2 knees	47 (25.0)	55 (28.9)	41 (21.9)	143 (25.3)
Length of diagnosis of osteoarthritis, *n (%)*				
<5 y	100 (53.8)	97 (53.0)	82 (44.3)	279 (50.4)
6–10 y	37 (19.9)	33 (18.0)	45 (24.3)	115 (20.8)
>10 y	49 (25.8)	53 (29.0)	58 (31.4)	160 (28.9)
Walking pain on flat surface, *n (%)*				
Moderate or lesser pain	143 (76.5)	142 (75.5)	126 (68.3)	412 (73.4)
Severe or extreme	44 (23.5)	46 (24.5)	59 (31.6)	149 (26.6)
Concurrent medications, *n (%)*				
Simple analgesics	17 (10.2)	21 (11.7)	18 (10.7)	66 (12.4)
NSAIDs	52 (31.3)	59 (32.8)	48 (28.4)	159 (29.9)
COX-2 selective inhibitors	41 (22.5)	52 (28.9)	50 (29.6)	143 (26.9)
Opioids	10 (5.5)	9 (5.0)	12 (7.1)	31 (5.8)
Outcomes				
WOMAC pain score‡	8.92 ± 3.42	8.90 ± 3.39	9.01 ± 3.70	8.94 ± 3.50
WOMAC function score§	31.31 ± 12.06	31.29 ± 12.00	32.48 ± 11.81	31.69 ± 11.96
Patient global assessment‖	2.95 ± 0.97	3.08 ± 0.88	2.94 ± 0.88	2.99 ± 0.91
SF-36 physical health score	48.69 ± 20.44	49.65 ± 19.92	46.08 ± 19.50	48.18 ± 19.99
6-min walk, *ft*	1150 ± 327	1130 ± 333	1118 ± 317	1133 ± 326

* There were no statistically significant differences among the 3 groups at baseline. Values expressed with a plus/minus sign are means ± SD. COX-2 = cyclooxygenase-2; NSAIDs = nonsteroidal anti-inflammatory drugs; SF-36 = 36-Item Short-Form Health Survey; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Denominators vary slightly because of missing data.
‡ Range, 0–20.
§ Range, 0–68.
‖ Range, 1–5.

SAS, version 9.0. We used the Markov chain Monte Carlo approach to impute all missing values on the basis of baseline demographic characteristics and pain and function scores. We used 5 randomly drawn imputations with the same mixed-model analysis method. We then used the MIANALYZE procedure to combine results and estimate appropriate regression coefficients and standard errors. We compared the estimated changes from baseline at each time point on all outcome measures with those observed without imputation. We also examined *P* values comparing treatment groups.

We compared regression coefficients and *P* values at each time point on the basis of the multiple imputation procedure versus the available data only by using mixed-model analyses modeling the within-patient covariate structure and including site as a random effect. For all outcomes at all time points, except as noted, the results of the multiple imputation analyses were very similar to those that used nonimputed data. The *P* values comparing true and sham acupuncture groups were also similar. Thus, we present only the results from the analyses that used all available data.

We conducted an additional exploratory analysis that compared the proportion of participants fulfilling the Outcome Measures in Rheumatoid Arthritis Clinical Trials–OsteoArthritis Research Society International (OMERACT-OARSI) responder index (28) at 26 weeks in the 3 treatment groups by using chi-square tests and by constructing risk ratios comparing each group with the sham acupuncture group.

Table 2. **Mean Change from Baseline in Participant Outcomes***

Week	Group	WOMAC and Patient Global Assessment						
		Participants, *n*	WOMAC Pain Score†	*P* Value‡	WOMAC Function Score†	*P* Value‡	Patient Global Assessment Score	*P* Value‡
4	True acupuncture	173	−2.22 ± 0.24	>0.2	−7.56 ± 0.78	0.15	0.13 ± 0.07	>0.2
	Sham acupuncture	163	−1.98 ± 0.25		−5.90 ± 0.66		0.10 ± 0.07	
	Education	124	−0.84 ± 0.26	<0.001	−4.65 ± 0.81	0.05	0.07 ± 0.09	>0.2
8	True acupuncture	169	−3.15 ± 0.29	0.18	−10.77 ± 0.90	0.01	0.30 ± 0.07	>0.2
	Sham acupuncture	161	−2.66 ± 0.26		−7.84 ± 0.76		0.14 ± 0.08	
	Education	125	−1.25 ± 0.30	<0.001	−5.30 ± 0.95	<0.001	0.04 ± 0.08	0.09
14	True acupuncture	158	−3.63 ± 0.31	<0.02	−12.18 ± 0.96	0.04	0.36 ± 0.08	>0.2
	Sham acupuncture	157	−2.68 ± 0.33		−9.40 ± 0.94		0.26 ± 0.08	
	Education	113	−1.54 ± 0.35	0.001	−5.62 ± 1.05	<0.001	0.15 ± 0.09	0.03
26	True acupuncture	142	−3.79 ± 0.33	<0.01	−12.42 ± 1.12	<0.01	0.45 ± 0.08	0.02
	Sham acupuncture	141	−2.92 ± 0.30		−9.88 ± 0.93		0.19 ± 0.09	
	Education	108	−1.69 ± 0.33	<0.01	−7.17 ± 1.07	0.01	0.22 ± 0.08	>0.2

* Test results and *P* values from mixed-model analysis of change from baseline, Toeplitz (banded) covariance matrix to control for within-participant correlation, clinical site as a random effect. Models include baseline value of the outcome variable, highly statistically significant in all cases. Values presented with a plus/minus sign are means ± SE. SF-36 = 36-Item Short-Form Health Survey; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Pain and function were the primary trial end points.
‡ *P* values compare true acupuncture and education groups with sham acupuncture group.

Role of the Funding Source

The National Center for Complementary and Alternative Medicine and the National Institute of Arthritis and Musculoskeletal and Skin Diseases provided funding for this study. The agencies had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Of the 735 participants assessed for eligibility, 165 were excluded from the trial, primarily because of the presence of other clinically significant diseases (35.2%), insufficient pain (24.2%), or no radiographic evidence of an osteophyte (**Figure**). Of the 570 participants who were randomly assigned, 27 were not available for the intention-to-treat analysis because they declined to be measured at baseline. In addition, 73 participants were medically disqualified, and 128 voluntarily withdrew sometime during the 6-month trial. Medical disqualification did not statistically significantly differ between groups; however, substantially fewer participants were available for assessment at 26 weeks in the education group (47%) than in the true acupuncture group (25%) or the sham control group (25%).

Among the 283 true and sham acupuncture participants who completed the trial, the mean number of sessions received was 22.7 of the 25 possible sessions (or 91% of the targeted regimen). (Adherence to acupuncture appointments did not statistically significantly differ between the true and sham groups.)

Most study participants were female (64%), white (69%), and 60 years of age or older (81%). No pretreatment differences existed among the 3 experimental groups with respect to any demographic characteristic, outcome, or medication usage variable (**Table 1**), suggesting that the randomization procedures produced comparable groups at baseline.

Table 2 presents the mean changes from baseline for the 5 study outcomes. A trend for the 3 groups as a whole was statistically significant (that is, the time main effect) to improve over time on all of the outcomes except the 6-minute walk. Of greater interest, however, are the differences in improvement in study outcomes observed between participants receiving true versus sham acupuncture at the different points in time.

Pain

While pain among participants who were receiving true acupuncture decreased more than in the sham group at all of the postbaseline assessments, this difference was not statistically significant at week 8. By week 14, the mean WOMAC pain score had decreased by 3.6 units in the acupuncture group (a 40% decrease from baseline) compared with −2.7 in the sham group ($P = 0.02$). These differences remained at week 26 ($P = 0.003$).

Function

The true acupuncture group's improvement in function from baseline was significantly greater than that of the sham control group at weeks 8 ($P = 0.01$), 14 ($P = 0.04$), and 26 ($P = 0.009$). A change of more than 12 units by 14 weeks is an almost 40% improvement from baseline.

Patient Global Assessment

Consisting of 1 item that asked participants how their knee osteoarthritis was affecting them, the patient global assessment showed no statistically significant difference in true versus sham acupuncture improvement until the final 26-week assessment (**Table 2**). At the conclusion of the trial, participants' changes from baseline were significantly greater (*es* = 0.26; $P = 0.02$) for those receiving true acu-

Table 2—**Continued**

SF-36 Physical Health			6-Minute Walk		
Participants, *n*	SF-36 Physical Health Score	*P* Value‡	Participants, *n*	6-Minute Walk Distance, *ft*	*P* Value‡
169	9.2 ± 1.4	>0.2	163	64.1 ± 18.0	>0.2
169	7.6 ± 1.2		156	67.7 ± 18.6	
126	4.3 ± 1.3	0.02	89	−1.0 ± 30.8	0.02
142	10.7 ± 1.6	0.21	136	74.2 ± 20.2	>0.2
141	8.2 ± 1.5		129	105.0 ± 21.4	
108	4.0 ± 1.5	0.01	75	−3.6 ± 40.8	<0.01

puncture (15%) than their sham counterparts (6%). However, the difference between groups was somewhat less and not significant in the imputed analysis ($P = 0.11$).

SF-36 Physical Function

The SF-36 was administered to trial participants only at baseline, week 8, and week 26. While the overall pattern of improvement mirrored that of the other outcome variables, changes in overall physical component score did not statistically significantly differ between the true versus sham acupuncture groups (**Table 2**).

Six-Minute Walk

We observed no statistically significant differences at any time point.

OMERACT-OARSI Responder Index

The proportion of participants who were classified as responders at 26 weeks was 98 of 186 (52%) in the true acupuncture group, 86 of 183 (47%) in the sham group ($P > 0.2$ compared with true), and 52 of 174 (30%) in the education group. These between-group differences were not significant for the true versus sham comparison, but the proportion of responders was significantly greater ($P < 0.001$) in both the true and sham acupuncture groups than in the education control group.

Masking Effectiveness

To evaluate the masking effectiveness of the sham acupuncture procedure, we asked participants in the acupuncture and sham groups to report which treatment they believed they were receiving at both 4 and 26 weeks: "true acupuncture," "sham acupuncture," or "uncertain." Most participants in both groups believed that they were receiving true acupuncture at both times, suggesting that the sham acupuncture procedure was a relatively credible blinding strategy. At 4 weeks, 67% in the true acupuncture group and 58% in the sham group believed that they were receiving true acupuncture ($P = 0.06$), and 25% and 33% were unsure, respectively. By the end of the trial, more individuals in the true group (75%) than in the sham group (58%) held this belief ($P = 0.003$), and 23% and 32% were unsure, respectively. Loss to follow-up did not differ between true and sham groups but was higher in both groups among those who believed they were receiving sham acupuncture at 4 weeks or who were unsure of their assignment (data not shown). As indicated in **Table 3**,

Table 3. **Relationship between Group Guesses at 26 Weeks and Western Ontario and McMaster Universities Osteoarthritis Index Pain and Function End Points***

End Point	Uncertain (*n* = 49)	Sham Acupuncture (*n* = 45)	True Acupuncture (*n* = 187)	*P* Value
Pain				
8 wk	−2.8 (−3.9 to −1.8)	−1.0 (−1.8 to −0.2)	−3.8 (−4.2 to −3.3)	<0.001
26 wk	−2.9 (−4.0 to −1.9)	−1.2 (−2.0 to −0.3)	−4.0 (−4.6 to −3.5)	<0.001
Function				
8 wk	−7.6 (−10.7 to −4.5)	−3.1 (−5.6 to −0.7)	−11.8 (−13.3 to −10.3)	<0.001
26 wk	−8.9 (−12.3 to −5.5)	−4.7 (−7.1 to −2.3)	−13.4 (−15.2 to −11.6)	<0.001

* Values in parentheses are 95% CIs.

Table 4. **Serious Adverse Events (*n* = 26) Reported during Trial**

Adverse Event	True Acupuncture (*n* = 190), *n*	Sham Acupuncture (*n* = 191), *n*	Education Control (*n* = 189), *n*
Heart disease	1	0	2
Cancer	2	0	0
Joint (not knee) surgery	0	0	2
Non–study-related injuries	3	1	1
Exacerbation of knee pain	0	1	0
Non–arthritis-related surgery	6	3	1
Stroke	1	0	0
Elevated blood pressure	0	0	1
Pneumonia	1	0	0
Total, *n (%)*	14 (7.4)	5 (2.6)	7 (3.7)

however, participant guesses on which treatment they were receiving were related to changes in WOMAC pain and function scores at both 8 and 26 weeks.

Safety

Twenty-six adverse events were reported for the 570 participants: 14 (7%) in the true acupuncture group, 5 (3%) in the sham control, and 7 (4%) in the education control (**Table** 4). Of the 14 adverse events observed in the true acupuncture group, none was interpreted as treatment-related, and the differences among groups did not reach statistical significance. In addition to adverse events, all participants were asked to report subjective symptoms that could be attributed to acupuncture (such as dizziness, nausea, and numbness) during the study. Changes in these symptoms after the baseline assessment did not statistically significantly differ among the 3 groups, and the incidence of these symptoms was quite low throughout the trial. A total of 73 medical disqualifications occurred: 17 (9%) in the true acupuncture group, 27 (14%) in the sham group, and 29 (15%) in the education control group. We included these participants' data in all analyses, although most often they declined our invitation to continue assessments after the cessation of treatment. The most common reasons for medical disqualification during the study were the receipt of intra-articular cortisone injections in the index knee and the development of medical conditions that were deemed by the study physician to contraindicate continued participation.

Concurrent Treatments

Participants continued to receive medical care during the study from their primary care physicians and were allowed to receive their usual medications. At baseline, for example, 11% of the participants were receiving a wide range of simple analgesics, 31% were taking nonselective NSAIDs, 28% were taking COX-2 selective inhibitors, and 6% were receiving an opioid. We tracked these 4 categories of medication usage at each assessment after baseline to ensure that any between-group outcome differences observed were not attributable to changes in concurrent medication use. We found no statistically significant differences between the proportions of participants in the true and sham groups who were using any of the 4 medication types at the 4-, 8-, 14-, or 26-week assessments, although participants in the education group were significantly more likely to be using both nonselective NSAIDs and COX-2 selective inhibitors after baseline than participants in the true acupuncture group. Since this latter finding would attenuate the pain and function differences observed between these 2 groups, however, we concluded that the positive differences reported in **Table 2** were not likely to be attributable to changes in medication patterns occurring over the course of the trial.

DISCUSSION

The results of our study extend those of our previous trial (19) and demonstrate that true traditional Chinese acupuncture is safe and effective for reducing pain and improving physical function in patients with symptomatic knee osteoarthritis who have moderate or greater pain despite background therapy with analgesic or anti-inflammatory therapy. We used a credible sham acupuncture group to control for the potential placebo effect in our trial. In addition, we included the recommended nonpharmacologic treatment (education) as a second control group (3). While the participants in the true acupuncture group were more likely to correctly guess their treatment, this masking procedure was reasonably successful in blinding participants in the sham control group since most participants believed that they were receiving true acupuncture (or were unsure) throughout the study. However, participants' differential awareness of group membership may have contributed to the positive results found. These between-group masking differences may have reflected the differential pain and function improvements due to the treatments themselves. In other words, because real acupuncture was benefiting its recipients, they, in turn, assumed that they were receiving real rather than sham treatment. We cannot be sure, however, what, if any, effects participants' guesses on group membership had on the overall trial results.

In any event, our trial ensured reasonable concealment of group allocation, the failure for which has been associated with biased estimates of treatment effects (29); provided evidence for the utility of the Center for Integrative Medicine sham procedure for use in acupuncture trials; contained adequate power (30); and adhered to the OARSI's recommendation that symptom relief be assessed for 24 weeks or more (31). Because of the educational control group's excessive attrition rate, coupled with the fact that its participants were not blinded to group membership, we feel that the true versus sham acupuncture contrasts are the more valid comparisons. We interpret the superiority of true compared with sham acupuncture in improvements in

pain and function as evidence of the treatment's efficacy, especially given the masking success achieved for the sham procedure. We note, however, that the statistically significant differences between the true and sham acupuncture groups in improvement in pain and function as measured by the WOMAC osteoarthritis index were not corroborated by the results of the exploratory analysis by using the OMERACT-OARSI responder index, in which 53% and 47% were considered to be responders at 26 weeks, respectively. This index was developed to separate participants receiving active treatments from those receiving placebo and has not been used before in a trial assessing the benefit of an adjunctive therapy in participants who are already receiving background therapy (28).

Although considerable attrition occurred over the 6-month study for all groups, this problem was not differential for the true and sham groups. We interpret this finding, coupled with the results of the analytic steps we took to study the differences between participants who dropped out of the trial versus those who completed it, as indicative that attrition did not confound the observed true versus sham differences. There is, however, no way to be absolutely certain that this problem did not affect our 26-week results.

We believe that our study is the largest randomized, placebo-controlled acupuncture trial to date and that it involved a more intensive acupuncture regimen (23 sessions) for a longer period (26 weeks) than any other trial. The 2 most carefully designed previous negative randomized, controlled trials of acupuncture in patients with osteoarthritis (16, 17) each included only 20 participants per group and administered fewer than 10 acupuncture treatments. While the duration of our acupuncture treatment may seem long, we used only 8 weeks of focused treatment, followed by a tapered schedule for maintenance purposes. This is not an uncommon practice in China. Additional research is needed to determine the minimum effective dosage of acupuncture for knee osteoarthritis.

It is interesting that the optimal acupuncture effects observed for our primary outcomes took a minimum of 8 weeks (which involved 16 acupuncture treatments) for function and 14 weeks for pain to manifest. This time course for response to therapy is similar to that observed for slow-acting symptomatic drugs, such as glucosamine, chondroitin sulfate, and avocado and soy unsaponifiable extracts (32), and, if replicable, has important implications for interpreting previous (and designing future) acupuncture trials. From a physiologic perspective, this delayed response is not consistent with the most commonly proposed mechanisms of acupuncture (for example, the release of neuropeptides or gate control theory).

If these results are valid, our trial has 2 important clinical implications. First, the absence of any observed treatment side effects attributable to either acupuncture needling or the use of electrical stimulation contrasts to current pharmacologic therapies for osteoarthritis that have side effects that may rival in severity the arthritis symptoms themselves. Second, observed acupuncture effects were achieved in addition to those of other viable osteoarthritis treatments, such as nonpharmacologic therapies and NSAIDs or COX-2 selective inhibitors, since study participants were free to pursue any therapy they or their physician desired. Thus, acupuncture may have an important role in adjunctive therapy as part of a multidisciplinary integrative approach to treating symptoms related to knee osteoarthritis (12).

From University of Maryland School of Medicine, Baltimore, Maryland.

Acknowledgments: The authors thank Mary Bahr, study coordinator; Jody Boone, arthritis educator; Marcos Hsu, ND, LAc, acupuncturist; Michelle Sittig and Deborah Taber, research assistants; Danuta Bujak, RN, CRNP, PhD, nurse practitioner; and Amy Martin Burns, administrative assistant, for their contributions.

Grant Support: By the National Center for Complementary and Alternative Medicine (National Institutes of Health Cooperative Agreement U01 AT-00171), with advice and encouragement by the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Brian Berman, MD, Center for Integrative Medicine, University of Maryland School of Medicine, 2200 Kernan Drive, Baltimore, MD 21207.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al.** Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum. 1998;41:778-99. [PMID: 9588729]

2. **Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, et al.** Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med. 2000;133:635-46. [PMID: 11033593]

3. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum. 2000;43:1905-15. [PMID: 11014340]

4. **Pendleton A, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JW, et al.** EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2000;59:936-44. [PMID: 11087696]

5. **Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, et al.** Osteoarthritis: new insights. Part 2: treatment approaches. Ann Intern Med. 2000;133:726-37. [PMID: 11074906]

6. **Altman RD.** Pain relief in osteoarthritis: the rationale for combination therapy [Editorial]. J Rheumatol. 2004;31:5-7. [PMID: 14705209]

7. **Hernández-Díaz S, García-Rodríguez LA.** Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. Am J Med. 2001; 110 Suppl 3A:20S-7S. [PMID: 11173046]

8. **Strand V, Hochberg MC.** The risk of cardiovascular thrombotic events with selective cyclooxygenase-2 inhibitors [Editorial]. Arthritis Rheum. 2002;47:349-55. [PMID: 12209478]

9. **Rao JK, Mihaliak K, Kroenke K, Bradley J, Tierney WM, Weinberger M.** Use of complementary therapies for arthritis among patients of rheumatologists.

Ann Intern Med. 1999;131:409-16. [PMID: 10498556]

10. **Bausell RB, Lee WL, Berman BM.** Demographic and health-related correlates to visits to complementary and alternative medical providers. Med Care. 2001;39:190-6. [PMID: 11176556]

11. **Berman BM, Bausell RB, Lee WL.** Use and referral patterns for 22 complementary and alternative medical therapies by members of the American College of Rheumatology: results of a national survey. Arch Intern Med. 2002;162:766-70. [PMID: 11926849]

12. **Hochberg MC.** Multidisciplinary integrative approach to treating knee pain in patients with osteoarthritis [Editorial]. Ann Intern Med. 2003;139:781-3. [PMID: 14597463]

13. **Wong TW, Fung KP.** Acupuncture: from needle to laser. Fam Pract. 1991; 8:168-70. [PMID: 1874364]

14. **Astin JA, Pelletier KR, Marie A, Haskell WL.** Complementary and alternative medicine use among elderly persons: one-year analysis of a Blue Shield Medicare supplement. J Gerontol A Biol Sci Med Sci. 2000;55:M4-9. [PMID: 10719766]

15. **Ezzo J, Hadhazy V, Birch S, Lao L, Kaplan G, Hochberg M, et al.** Acupuncture for osteoarthritis of the knee: a systematic review. Arthritis Rheum. 2001;44:819-25. [PMID: 11315921]

16. **Gaw AC, Chang LW, Shaw LC.** Efficacy of acupuncture on osteoarthritic pain. A controlled, double-blind study. N Engl J Med. 1975;293:375-8. [PMID: 1097921]

17. **Takeda W, Wessel J.** Acupuncture for the treatment of pain of osteoarthritic knees. Arthritis Care Res. 1994;7:118-22. [PMID: 7727550]

18. **Berman BM, Lao L, Greene M, Anderson RW, Wong RH, Langenberg P, et al.** Efficacy of traditional Chinese acupuncture in the treatment of symptomatic knee osteoarthritis: a pilot study. Osteoarthritis Cartilage. 1995;3:139-42. [PMID: 7584319]

19. **Berman BM, Singh BB, Lao L, Langenberg P, Li H, Hadhazy V, et al.** A randomized trial of acupuncture as an adjunctive therapy in osteoarthritis of the knee. Rheumatology (Oxford). 1999;38:346-54. [PMID: 10378713]

20. **Lao L, Bergman S, Langenberg P, Wong RH, Berman B.** Efficacy of Chinese acupuncture on postoperative oral surgery pain. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995;79:423-8. [PMID: 7614199]

21. **Lao L, Bergman S, Hamilton GR, Langenberg P, Berman B.** Evaluation of acupuncture for pain control after oral surgery: a placebo-controlled trial. Arch Otolaryngol Head Neck Surg. 1999;125:567-72. [PMID: 10326816]

22. **Cheng X, ed.** Chinese Acupuncture and Moxibustion. Beijing, China: Foreign Languages Pr; 1999.

23. **O'Connor J, Bensky D, trans-eds.** Acupuncture: A Comprehensive Text. Chicago: Eastland Pr; 1981.

24. **Lorig K, González VM, Laurent DD, Morgan L, Laris BA.** Arthritis self-management program variations: three studies. Arthritis Care Res. 1998;11:448-54. [PMID: 10030176]

25. **Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW.** Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833-40. [PMID: 3068365]

26. **Ware JE Jr, Sherbourne CD.** The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83. [PMID: 1593914]

27. **Meenan RF, Mason JH, Anderson JJ, Guccione AA, Kazis LE.** AIMS2. The content and properties of a revised and expanded Arthritis Impact Measurement Scales Health Status Questionnaire. Arthritis Rheum. 1992;35:1-10. [PMID: 1731806]

28. **Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al.** OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage. 2004;12:389-99. [PMID: 15094138]

29. **Schulz KF, Chalmers I, Hayes RJ, Altman DG.** Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995;273:408-12. [PMID: 7823387]

30. **Bausell RB, Li YF.** Power Analysis for Experimental Research: A Practical Guide for the Biological, Medical and Social Sciences. Cambridge, United Kingdom: Cambridge Univ Pr; 2002.

31. **Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, et al.** Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. Osteoarthritis Cartilage. 1996;4:217-43. [PMID: 11048620]

32. **Hochberg MC, Dougados M.** Pharmacological therapy of osteoarthritis. Best Pract Res Clin Rheumatol. 2001;15:583-93. [PMID: 11567541]

Current Author Addresses: Drs. Berman, Lao, Lee, and Gilpin: Center for Integrative Medicine, University of Maryland School of Medicine, 2200 Kernan Drive, Baltimore, MD 21207.
Dr. Langenberg: EPM Gender Based, 102 A, HH, University of Maryland School of Medicine, 660 West Redwood Street, Baltimore, MD 21201.
Dr. Hochberg: University of Maryland School of Medicine, 10 South Pine Street, MSTF 834, Baltimore, MD 21201.

Author Contributions: Conception and design: B. Berman, L. Lao, P. Langenberg, M.C. Hochberg.
Analysis and interpretation of the data: B. Berman, P. Langenberg, W.L. Lee, A.M.K. Gilpin, M.C. Hochberg.
Drafting of the article: B. Berman, L. Lao, P. Langenberg.
Critical revision of the article for important intellectual content: B. Berman, L. Lao, P. Langenberg, A.M.K. Gilpin, M.C. Hochberg.
Final approval of the article: B. Berman, L. Lao, P. Langenberg, W.L. Lee, A.M.K. Gilpin, M.C. Hochberg.
Statistical expertise: P. Langenberg.
Obtaining of funding: B. Berman, L. Lao.
Administrative, technical, or logistic support: L. Lao.
Collection and assembly of data: W.L. Lee.