Acupuncture for Patients With Migraine
A Randomized Controlled Trial

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Context Acupuncture is widely used to prevent migraine attacks, but the available evidence of its benefit is scarce.

Objective To investigate the effectiveness of acupuncture compared with sham acupuncture and with no acupuncture in patients with migraine.

Design, Setting, and Patients Three-group, randomized, controlled trial (April 2002-January 2003) involving 302 patients (88% women), mean (SD) age of 43 (11) years, with migraine headaches, based on International Headache Society criteria. Patients were treated at 18 outpatient centers in Germany.

Interventions Acupuncture, sham acupuncture, or waiting list control. Acupuncture and sham acupuncture were administered by specialized physicians and consisted of 12 sessions per patient over 8 weeks. Patients completed headache diaries from 4 weeks before to 12 weeks after randomization and from week 21 to 24 after randomization.

Main Outcome Measures Difference in headache days of moderate or severe intensity between the 4 weeks before and weeks 9 to 12 after randomization.

Results Between baseline and weeks 9 to 12, the mean (SD) number of days with headache of moderate or severe intensity decreased by 2.2 (2.7) days from a baseline of 5.2 (2.5) days in the acupuncture group compared with a decrease to 2.2 (2.7) days from a baseline of 5.0 (2.4) days in the sham acupuncture group, and by 0.8 (2.0) days from a baseline if 5.4 (3.0) days in the waiting list group. No difference was detected between the acupuncture and the sham acupuncture groups (0.0 days, 95% confidence interval, –0.7 to 0.7 days; $P=.96$) while there was a difference between the acupuncture group compared with the waiting list group (1.4 days; 95% confidence interval; 0.8-2.1 days; $P<.001$). The proportion of responders (reduction in headache days by at least 50%) was 51% in the acupuncture group, 53% in the sham acupuncture group, and 15% in the waiting list group.

Conclusion Acupuncture was no more effective than sham acupuncture in reducing migraine headaches although both interventions were more effective than a waiting list control.

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MIGRAINE IS A COMMON AND disabling condition that typically manifests as attacks of severe, pulsating, 1-sided headaches, often accompanied by nausea, phonophobiaor or photophobia. Population-based studies suggest that 6% to 7% of men and 15% to 18% of women experience migraine headaches.[1,2] Although in most cases it is sufficient to treat acute headaches, many patients require interval treatment as attacks occur often or are insufficiently controlled. Drug treatment with β-blockers, calcium antagonists, or other agents has been shown to reduce the frequency of migraine attacks; however, the success of treatment is usually modest and tolerability often suboptimal.[3]

Acupuncture is widely used for preventing migraine attacks although its effectiveness has not yet been fully established.[4] Since 2001, German social health insurance companies have reimbursed accredited physicians who provide acupuncture treatment for chronic pain. By December 2004 more than 2 million patients had been treated with acupuncture, about a third of these had migraine or tension-type headaches. In this study, the Acupuncture Randomized Trial (ART-Migraine), we investigated whether acupuncture reduced headache frequency more effectively than sham acupuncture or no acupuncture in patients with migraines.

METHODS

Design

The methods of this trial have been described in detail elsewhere.[5] The

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ART-Migraine was a randomized, multicenter trial comparing acupuncture, sham acupuncture, and a no-acupuncture waiting list condition. The additional no-acupuncture waiting list control was included because sham acupuncture cannot be substituted for a physiologically inert placebo. Patients in the acupuncture groups were blinded to which treatment they received. Analysis of headache diaries was performed by 2 blinded evaluators. The study duration per patient was 28 weeks: 4 weeks before randomization, the baseline; 8 weeks of treatment; and 16 weeks of follow-up. Patients allocated to the waiting list received true acupuncture after 12 weeks and were also followed up for 24 weeks after randomization (to investigate whether changes were similar to those in patients receiving immediate acupuncture).

After the baseline period patients meeting the inclusion criteria were randomly stratified by center (block size 12 not known to trial centers) in a 2:1:1 ratio (acupuncture:sham acupuncture: waiting list) using a centralized telephone randomization procedure (random list generated with Sample Size 2.0).[6] The 2:1:1 ratio was used to facilitate recruitment and increase the compliance of trial physicians. All study participants provided written informed consent. The study was performed according to common guidelines for clinical trials (Declaration of Helsinki, International Conference on Harmonization–Good Clinical Practice including certification by external audit). The protocol had been approved by all relevant local ethics review boards.

Patients

To be included, patients had to have a diagnosis of migraine, with or without aura, according to the criteria of the International Headache Society[7]; 2 to 8 migraine attacks per month during the last 3 months and during the baseline period; be aged 18 to 65 years; had had migraines for at least 12 months; had completed baseline headache diary; and provided written informed consent. Main exclusion criteria were interval headaches or additional tension-type headache on more than 10 days per month; inability to distinguish between migraine attacks and additional tension-type headache; secondary headaches; start of headaches after age 50 years; use of analgesics on more than 10 days per month; prophylactic headache treatment with drugs during the last 4 weeks; and any acupuncture treatment during the last 12 months or at any time if performed by the participating trial physician.

Most participants were recruited through reports in local newspapers; some patients spontaneously contacted the trial centers.

Interventions

Study interventions were developed by consensus of acupuncture experts and societies and were provided by physicians trained (at least 140 hours, median 500 hours) and experienced (median 10 years) in acupuncture. Both the acupuncture and sham acupuncture treatment consisted of 12 sessions of 30 minutes' duration, each administered over a period of 8 weeks (preferably 2 sessions in each of the first 4 weeks, followed by 1 session per week in the remaining 4 weeks).

Acupuncture treatment was semistandardized. All patients were treated at what are called basic points (gallbladder 20, 40, or 41 or 42, Du Mai–governing vessel 20, liver 3, San Jiao 3 or 5, extra point Taiyang) bilaterally unless explicit reasons for not doing so were given. Additional points could be chosen individually, according to patient symptoms.[5] Sterile disposable 1-time-use needles had to be used, but physicians could choose needle length and diameter. Physicians were instructed to achieve "de Qi" (in which patients experience an irradiating feeling considered to be indicative of effective needling) if possible, and needles were stimulated manually at least once during each session. The total number of needles was limited to 25 per treatment.

Number, duration, and frequency of the sessions in the sham acupuncture group were the same as for the acupuncture group. In each session, at least 5 out of 10 predefined distant nonacupuncture points (see Melchart et al[5] for details) were needled bilaterally (at least 10 needles) and superficially using fine needles (ie, minimal acupuncture). "De Qi" and manual stimulation of the needles were avoided. All acupuncturists received oral instructions, a videotape, and a brochure with detailed information on sham acupuncture.

Patients in the waiting list control group did not receive any prophylactic treatment for their headaches for a period of 12 weeks after randomization. After that period they received 12 sessions of the acupuncture treatment described above.

All patients were allowed to treat acute headaches as needed. Attack treatment should follow the guidelines of the German Migraine and Headache Society[8] and had to be documented in the headache diary.

Patients were informed with respect to acupuncture and sham acupuncture in the study as follows: "In this study, different types of acupuncture will be compared. One type is similar to the acupuncture treatment used in China. The other type does not follow these principles, but has also been associated with positive outcomes in clinical studies."

Outcome Measurement

All patients completed headache diaries for 4 weeks before randomization (baseline phase), during the 12 weeks after randomization, and during the weeks 21 to 24 after randomization. In addition, patients were asked to complete a modified version of the pain questionnaire of the German Society for the Study of Pain[9] before treatment, after 12 weeks, and after 24 weeks. The questionnaire includes questions on sociodemographic characteristics, numerical rating scales for pain intensity, questions on workdays lost, global assessments, etc, as well as the following validated scales: (1) the German version of the Pain Disability Index[10]; (2) a scale for assessing emotional aspects of pain (Schmerzempfindungsskala

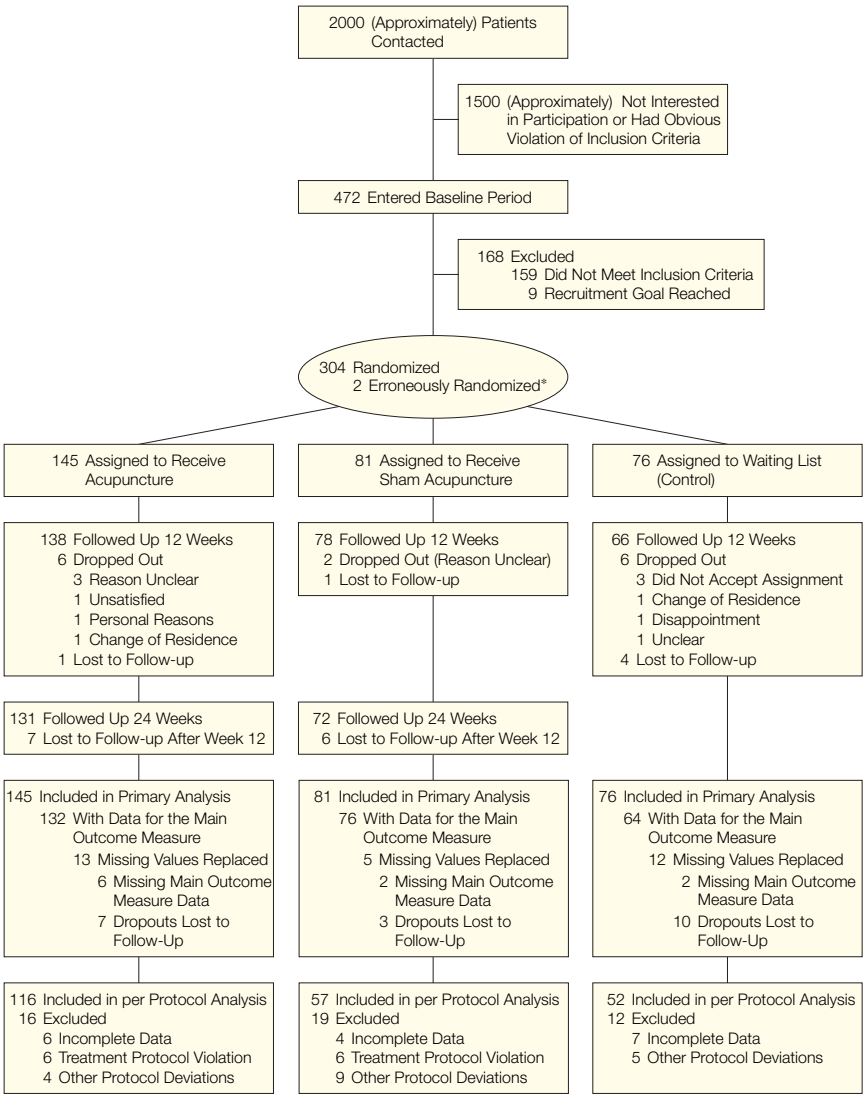
SES)[11]; (3) the depression scale Allgemeine Depressionskalla[12]; (4) the German version of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) to assess health-related quality of life.[13]

Primary outcome measure was the difference in number of days with headache of moderate or severe intensity between the 4 weeks before randomization (baseline phase) and weeks 9 to 12 after randomization. Predefined secondary outcomes included the number of migraine attacks (episodes of migraine headaches separated by pain-free intervals of at least 48 hours), total number of headache days, proportion of treatment responders, and days with medication.

To test blinding to treatment and to assess the credibility of the respective treatment methods, patients completed a credibility questionnaire after the third acupuncture session.[14] At the end of the study, patients were asked whether they thought that they had received acupuncture following the principles of Chinese medicine or the other type of acupuncture.

Physicians documented acupuncture treatment, serious adverse events and adverse effects for each session. Adverse effects were also reported by patients at the end of week 12.

Figure 1. Trial Flow Diagram



*Although 2 patients assigned to the acupuncture group came only to the initial examination but did not return at the end of the baseline phase, one of the large study centers erroneously registered them for randomization. According to the analysis plan the intent-to-treat population comprised only patients with baseline data.

Statistical Analysis

Confirmatory testing of the primary outcome measure (using SPSS 11.5, SPSS Inc, Chicago, Ill) was based on the intention-to-treat population, replacing missing data by baseline values (thus, setting differences compared with baseline to zero). A priori ordered 2-sided null hypotheses to be tested were (1) the primary outcome measure in the acupuncture group = outcome in waiting list; and (2) outcome in the acupuncture group = outcome in the sham acupuncture group. For each of the hierarchical hypotheses, we used the *t* test with a significance level of $P<.05$, thus testing in a first step whether acupuncture is more efficacious in reducing the number of days with moderate or severe headache than no treatment and in a second step (only if the first null hypothesis was rejected) whether acupuncture is more efficacious than sham acupuncture. Moreover, an analysis of covariance with additional covariates of age at randomization and sex was performed to account for potential baseline differences. Exploratory analyses (2-sided *t* tests and Fisher exact test for pairwise comparisons of groups without adjustment for multiple testing) based on all available data without replacing missing data are reported for secondary outcome measures. An additional per-protocol analysis was performed including only patients without major protocol violations until week 12.

Due to the positive previous evidence regarding acupuncture for headache[4] and the nature of the question posed by the German health authorities (See "Role of the Sponsor" in the Acknowledgment section) original sample-size calculations were based on 1-sided

testing. Under this premise the study was planned to have a power of 80% to detect a group difference of 1 day with moderate or severe headache with assumed SDs of 2.5 days (thus an effect size of 0.4), assuming a 20% dropout rate.[5] However, we later decided to use 2-sided testing to comply better with common standards.

RESULTS

Between April 2002 and January 2003 approximately 2000 patients with headaches expressed interest in participating in the study (FIGURE 1), 472 entered the 4-week baseline period, and 304 were randomly assigned. At one of the large study centers, 2 patients were randomly assigned erroneously because they had only come to the initial examination and never returned for the end of the baseline phase. The intent-to-treat population comprised all remaining 302 patients (145 acupuncture, 81 sham acupuncture, 76 waiting list) recruited in 18 outpatient centers. Seven patients (5%) in the acupuncture group, 3 (4%) in the sham acupuncture group, and 10 (13%) in the waiting list group withdrew or were lost to follow-up at week 12 ($P = .03$, χ^2 test). Another 10 patients (6 acupuncture, 2 sham acupuncture, 2 waiting list) did not complete the headache diary in a manner that allowed extraction of the primary outcome measure, so valid data at week 12 were available for 132 patients (91%) in the acupuncture group, 76 (94%) in the sham acupuncture group, and 64 (84%) in the waiting list group. At week 24, headache diary data were available for 131 (90%) of patients in the acupuncture group and 72 (89%) in the sham acupuncture group.

Groups were comparable at baseline (TABLE 1). A significant difference was only found for the physical health summary scale of the SF-36 (less impairment in the sham acupuncture group). The mean (SD) number of needles used per session was 17 (5) in the acupuncture group and 11 (3) in the sham acupuncture group. After 3 treatment sessions patients rated the credibility of acupuncture and sham acupuncture very highly and almost identically (TABLE 2). By the end of the study, patients' ability to guess correctly their allocation status differed significantly between the groups.

Between baseline and week 9 to 12 the number of days with headache of moderate or severe intensity decreased by a mean (SD) of 2.2 (2.7) days in the acupuncture group vs 2.2 (2.7) days in the sham acupuncture group and 0.8 (2.2) days in the waiting list group (difference acupuncture vs sham acupuncture, 0.0 days; 95% confidence interval [CI], –0.7 to 0.7 days; $P = .96$; acupuncture vs waiting list, 1.4 days, 95% CI, 0.8 to 2.1 days; $P < .001$; 2-sided confirmatory testing, intent-to-treat population with missing values replaced). The results were similar if the analysis was restricted to patients providing diary data and if baseline values were entered in the analysis of covariance as covariates. Additionally, the per-protocol analysis showed similar results. The proportion of responders (reduction of headache days with moderate or severe pain by at least 50%) was 51% in the acu-

Table 1. Baseline Characteristics

	All Patients (N = 302)	Acupuncture (n = 145)	Sham Acupuncture (n = 81)	Waiting List (n = 76)
Women, No. (%)	267 (88)	129 (89)	73 (90)	65 (86)
Age, mean (SD), y	42.6 (11.4)	43.3 (11.8)	41.3 (10.2)	42.5 (11.8)
Body mass index, mean (SD)	24.0 (4.1)	23.9 (4.1)	23.6 (4.0)	24.7 (4.4)
Migraine, No. (%)*				
Diagnosis				
Migraine without aura	226 (75)	109 (75)	62 (77)	55 (72)
Migraine with aura	87 (29)	40 (28)	23 (28)	24 (32)
Duration of disease, mean (SD), y	20.2 (11.8)	20.9 (12.1)	19.2 (11.7)	19.7 (11.3)
Previous acupuncture (for any condition), No. (%)	121 (40)	63 (43)	30 (37)	28 (37)
Headache symptoms, mean (SD), d				
Moderate to severe headache	5.2 (2.6)	5.2 (2.5)	5.0 (2.4)	5.4 (3.0)
Headache	8.2 (3.7)	8.3 (3.4)	8.3 (3.6)	8.0 (4.3)
Accompanying symptoms	4.7 (3.0)	4.7 (2.8)	4.7 (3.0)	5.0 (3.3)
Activities impaired	2.8 (2.2)	2.7 (2.2)	3.0 (2.1)	2.9 (2.5)
Medication needed	4.9 (2.8)	5.0 (2.8)	4.8 (2.6)	4.9 (2.8)
Migraine attacks	2.8 (1.2)	2.8 (1.2)	2.8 (1.2)	2.8 (1.2)
Attack medication use during baseline phase, No. (%)				
Triptans	91 (30)	40 (28)	24 (30)	27 (36)
Ergotamines	6 (2)	2 (1)	2 (2)	2 (3)
Analgesics	220 (73)	103 (71)	64 (79)	53 (70)
Combinations	55 (18)	30 (21)	11 (14)	14 (19)
Pain, mean (SD), SES, *t* standard score				
Affective	55.9 (8.8)	55.4 (9.0)	56.5 (8.9)	56.1 (8.3)
Sensoric	55.1 (8.7)	54.7 (8.7)	54.8 (8.2)	56.2 (9.2)
Disability, mean (SD), PDI	34.4 (16.6)	32.8 (15.5)	35.8 (17.9)	36.2 (16.9)
Health status, mean (SD)				
Physical, SF-36†	42.1 (7.5)	41.6 (7.7)	44.0 (6.6)	41.2 (7.8)
Mental, SF-36†	47.5 (9.9)	47.6 (10.1)	47.2 (10.0)	47.5 (9.5)
Depression, ADS, *t* standard score	49.4 (8.9)	50.3 (8.6)	48.5 (9.0)	48.6 (9.5)
Average pain rating scale, mean (SD)‡	5.6 (1.7)	5.6 (1.6)	5.6 (1.6)	5.8 (1.8)

Abbreviations: ADS, Allgemeine Depressionsskala, a depression scale; PDI, pain disability index; SES, Schmerzempfindungsskala, a questionnaire for assessing the emotional aspects of pain; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.
*Eleven patients had both migraine with and without aura.
†Higher values indicate better status.
‡Rating scale 0 to 10, with 0 being no pain and 10 being excruciating.

puncture group, 53% in the sham acupuncture group, and 15% in the waiting list group.

Compared with the waiting list control group, patients receiving acupuncture or sham acupuncture fared significantly better for most secondary outcome measures; however, there were no significant differences between the acupuncture group and the sham acupuncture group (TABLE 3). Response differences in the waiting list group became apparent after the first 4 weeks of treatment and increased until week 12 (FIGURE 2).

The improvements observed in the acupuncture groups persisted during the follow-up period (TABLE 4). Results in the sham acupuncture group tended to be slightly better than those in the acupuncture group, but the differences were not significant. The patients in the waiting list group who received acupuncture in weeks 13 to 20 showed similar improvements after treatment as those who had received immediate treatment (Figure 2).

Within the 24 weeks after randomization, 7 participants experienced serious adverse events (4 acupuncture, 1 sham acupuncture, 2 waiting list). All cases were hospital stays considered unrelated to study condition and intervention (3 had elective surgery, knee surgery after household injury, salpin-

Table 2. Patient Rating of Treatment Credibility and Guess of Treatment Type*

	Acupuncture		Sham Acupuncture		
	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)	*P* Value†
Credibility After Third Session					
Improvement expected	142	4.9 (0.9)	80	4.9 (0.9)	.88
Recommendation to others	142	5.5 (0.9)	80	5.5 (0.8)	.66
Treatment logical	142	4.9 (1.1)	80	4.9 (1.1)	.98
Effective also for other diseases	142	5.5 (0.8)	80	5.6 (0.7)	.35
Treatment Guess at End of Week 24, No. (%)					
No. of patients	129		72		
Chinese acupuncture		82 (64)		30 (42)	<.001
Other type of acupuncture		17 (13)		26 (36)	
Don't know		30 (23)		16 (22)	

*Credibility rating scale with 0 for sham and 6 for maximal agreement.
†*P* values derived from 2-sided *t* tests or χ^2 tests.

Table 3. Secondary Outcomes

	Acupuncture	Sham Acupuncture	Waiting List	Acupuncture vs Sham Acupuncture, Δ (95% CI)	*P* Value*	Acupuncture vs Waiting List, Δ (95% CI)	*P* Value*
Headache Diary Weeks 9 to 12							
Symptoms experienced, mean (SD), d							
Moderate to severe headache	2.8 (2.3)	2.6 (2.4)	4.3 (2.2)	0.2 (–0.5 to 0.9)	.58	–1.5 (–2.2 to –0.8)	<.001
Headache	4.9 (3.4)	4.7 (3.4)	6.3 (3.6)	0.1 (–0.8 to 1.1)	.76	–1.4 (–2.5 to –0.4)	.008
Medication use	3.2 (3.0)	3.4 (2.9)	4.4 (3.6)	–0.2 (–1.0 to 0.6)	.65	–1.2 (–2.2 to –0.2)	.01
Accompanying symptoms	2.3 (2.5)	2.3 (2.6)	3.9 (2.6)	0.0 (–0.7 to 0.7)	.99	–1.6 (–2.4 to –0.9)	<.001
Activities impaired	1.2 (1.6)	1.3 (1.8)	2.3 (1.9)	0.2 (–0.6 to 0.3)	.53	–1.2 (–1.7 to –0.7)	<.001
No. of mean (SD) migraine attacks	1.5 (1.2)	1.6 (1.3)	2.3 (1.1)	–0.1 (–0.5 to 0.2)	.48	-0.8 (–1.1 to –0.4)	<.001
				RR (95% CI)		**RR (95% CI)**	
Symptom reduction, No. (%)							
≥50% Days of moderate to severe headache†	74 (51)	43 (53)	11 (15)	0.96 (0.74 to 1.25)	.78	3.53 (2.00 to 6.23)	<.001
≥50% Of migraine attacks†	78 (54)	43 (53)	13 (17)	1.01 (0.79 to 1.31)	>.99	3.14 (1.87 to 5.28)	<.001
Questionnaire Responses at End of Week 12							
				Δ (95% CI)		**Δ (95% CI)**	
Pain, mean (SD,) SES, *t* standard scores							
Affective	49.3 (10.9)	49.6 (10.7)	54.6 (9.6)	–0.3 (–3.3 to 2.8)	.85	–5.3 (–8.5 to –2.1)	.001
Sensoric	51.5 (10.4)	50.7 (10.0)	56.1 (10.5)	0.8 (–2.1 to 3.7)	.60	–4.6 (–7.8 to –1.4)	.005
Disability, mean (SD), PDI	20.7 (16.6)	20.2 (5.7)	32.9 (17.1)	0.5 (–4.1 to 5.1)	.82	–12.2 (–17.3 to –7.1)	<.001
Health status, mean (SD)							
Physical, SF-36‡	46.7 (7.5)	47.5 (7.0)	42.5 (6.6)	–0.8 (–2.9 to 1.3)	.44	4.3 (2.0 to 6.5)	<.001
Mental, SF-36‡	48.6 (8.8)	47.6 (9.6)	47.7 (10.6)	0.9 (–1.6 to 3.5)	.47	0.8 (–2.0 to 3.7)	.56
Depression, mean (SD) ADS, *t* standard scores	46.4 (8.6)	47.2 (10.9)	48.4 (9.8)	–1.9 (–4.8 to 0.9)	.18	–0.7 (–3.5 to 2.1)	.60
Average pain rating scale, mean (SD)§	3.7 (2.0)	3.6 (2.1)	5.6 (2.1)	0.1 (–0.5 to 0.6)	.87	–1.9 (–2.5 to –1.3)	<.001

Abbreviations: ADS, Allgemeine Depressionsskala depression scale; CI, confidence interval; Δ, mean difference between groups; PDI, Pain Disability Index; RR, responder ratio, proportion responders acupuncture/proportion responders control; SES, Schmerzempfindungsskala, a questionnaire for assessing the emotional aspects of pain; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.
*Exploratory *P* values from 2-sided *t* tests or Fisher exact test; percentages are column percentages.
†Responder proportions were calculated considering all patients with missing data as nonresponders (145 acupuncture group, 81 sham acupuncture group, and 76 waiting list group.
‡Higher values indicate better status; minor discrepancies between differences calculated from group means presented in the table and Δ are due to rounding.
§Rating scale of 0 to 10, with 0 being no pain and 10 being excruciating.

gitis, hypertensive crisis, diagnostic procedures). Thirty-six of 144 (25%) patients who had received at least 1 acupuncture treatment reported a total of 37 adverse effects, and 13 of 81 (16%) receiving sham acupuncture reported a total of 14 adverse effects ($P=.13$, Fisher exact test). Ten participants in the acupuncture vs 2 in the sham acupuncture groups reported that the treatment triggered migraine attacks or headache, 6 vs 1 reported fatigue, and 4 vs 2 reported hematoma, respectively

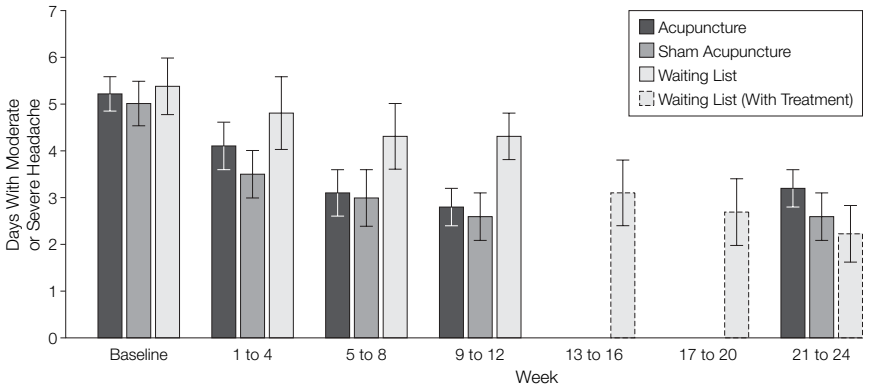
COMMENT

In this randomized trial, acupuncture was no more effective than sham acupuncture in reducing migraine headaches although both interventions were more effective than a waiting list control. Our study is, to date, one of the largest and most rigorous trials on the efficacy of acupuncture. The advantages to this study include a protocol based on current guidelines for migraine trials,[15] strictly concealed central randomization, assessment of the credibility of interventions, blinded diary evaluation, interventions based on expert consensus, and provision of care delivered by qualified and experienced medical acupuncturists. Our study also had high follow-up rates.

One potential limitation of the study is that participants probably had a more positive attitude toward acupuncture than the typical patient with migraines although experiences from ongoing reimbursement programs in Germany show that a large number of patients with chronic pain seek acupuncture treatment. Dropout rates in our study were low compared with other migraine prevention trials.[3] However, more patients in the waiting list group discontinued participation in the study after randomization than did those in the other 2 groups. This was probably due to disappointment about having to wait another 12 weeks for treatment after the 4-week baseline phase.

When patients were asked at the end of the trial to guess to which group they had been assigned, the patients' answers differed significantly between the

Figure 2. Number of Days With Moderate to Severe Headache



Error bars indicate 95% confidence intervals.

Table 4. Follow-up Data

	Acupuncture	Sham Acupuncture	Acupuncture vs Sham Acupuncture, Δ (95%CI)	*P* Value*
Headache Diary Weeks 21 to 24				
Symptoms experienced, mean (SD), d				
Moderate to severe headache	3.2 (2.5)	2.6 (2.1)	0.5 (–0.2 to 1.2)	.13
Headache	5.2 (3.3)	4.8 (3.1)	0.4 (–0.6 to 1.3)	.42
Medication	3.6 (3.7)	3.4 (2.5)	0.1 (–0.8 to 1.1)	.76
Accompanying symptoms	2.3 (2.5)	2.5 (2.5)	–0.1 (–0.8 to 0.6)	.72
Activities impaired	1.3 (1.8)	1.5 (2.0)	–0.2 (–0.7 to 0.3)	.44
Migraine attacks, mean (SD)	1.8 (1.4)	1.6 (1.2)	0.2 (–0.3 to 0.5)	.55
			RR (95%CI)	
Symptom reduction, No. (%)†				
≥50% Days of moderate to severe headache	66 (46)	42 (52)	0.88 (0.67 to 1.16)	.41
≥50% Days of migraine attacks	64 (44)	39 (48)	0.92 (0.69 to 1.23)	.58
Questionnaire Response at the End of Week 24				
			Δ (95%CI)	
Pain, mean (SD), SES, *t* standard scores				
Affective	48.6 (11.3)	47.0 (10.3)	1.56 (–1.6 to 4.8)	.33
Sensoric	51.7 (11.2)	49.6 (9.8)	2.0 (–1.1 to 5.2)	.20
Disability, mean (SD), PDI	17.4 (15.5)	15.5 (14.6)	2.0 (–2.4 to 6.4)	.38
Health status, mean (SD)‡				
Physical, SF-36	46.7 (7.0)	48.8 (7.3)	–2.1 (–4.2 to 0.0)	.05
Mental, SF-36	49.4 (9.0)	47.7 (9.8)	1.7 (–1.0 to 4.4)	.22
Depression, mean (SD), ADS, *t* standard scores	45.8 (9.1)	46.1 (9.7)	–0.3 (–3.1 to 2.4)	.82
Average pain, mean (SD), rating scale	3.8 (2.1)	3.4 (2.0)	0.4 (–0.2 to 1.0)	.24

Abbreviations: ADS, Allgemeine Depressionsskala, depression scale; CI, confidence interval; Δ, mean difference between groups; PDI, pain disability index; RR, responder ratio (proportion responders acupuncture/proportion responders control); SES, Schmerzempfindungsskala, questionnaire for assessing the emotional aspects of pain; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.
*Exploratory *P* values from 2-sided *t* tests or Fisher exact test.
†Responder proportions were calculated considering all patients with missing data as nonresponders (145, acupuncture group; 81, sham acupuncture group).
‡Higher values indicate better status; minor discrepancies between differences calculated from group means presented in the table and Δ are due to rounding.

acupuncture and sham acupuncture groups, which indicates some degree of unblinding. However, the results of the credibility assessment and overall findings of our trial make it unlikely that the comparison between acupuncture and sham acupuncture has been severely biased by unblinding.

In this study, it was not possible to blind waiting list patients. Therefore, we cannot rule out that the difference between acupuncture and sham acupuncture is overestimated due to bias. However, there are several arguments that could explain why the influence of bias should be limited. There was a significant improvement over time in the waiting list group in the first 12 weeks. This was probably due to the natural course of the disease or the general effect of being in a study (Hawthorne effect). This improvement, however, makes it unlikely that patients in the waiting list group reported negatively biased data in their diary. Analgesic use was lower in the acupuncture group and sham acupuncture group, thereby making an influence of effective cointerventions unlikely. Follow-up data confirmed the improvements observed after treatment. After completion of the treatment, patients had no further contact with acupuncturists. In addition, patients received and sent diaries and questionnaires directly to the study center, decreasing the likelihood of positively biased diary data.

The lack of differences between acupuncture and sham acupuncture in our study indicates that point location and other aspects considered relevant for acupuncture did not make a difference. To some extent, this finding contradicts current evidence in the literature. A number of small, mostly single-center trials have compared acupuncture with a variety of sham interventions.[4] Although the results of these trials were not fully consistent, they suggested that, overall, acupuncture is superior to sham interventions. We cannot rule out that the acupuncture interventions used in some of the older studies were more appropriate for the treatment of migraine. Nevertheless, we are confident that the consensus-based, semistandardized strategy in our multicenter trial represents a suitable intervention. Another potential explanation for the discrepancy in findings could be an overestimation of effects over sham controls in the smaller, older studies due to bias or chance.

An interesting finding of our trial is the strong response to sham acupuncture. The improvement over and the differences compared with the waiting list group are clearly clinically relevant. The number of days with moderate or severe headache and the frequency of migraine attacks were reduced by 50% or more compared with baseline in half of the patients and the improvement persisted over several months. This response rate is comparable with that observed during treatment with medications proven to be effective migraine prophylaxis, whereas response rates in placebo groups are typically around 30%.[3,16-18] Also, the effect of sham acupuncture over waiting list in our trial is larger than that found in a recent meta-analysis of pain trials including both a placebo and a no treatment control.[19] The strong response to sham acupuncture in our trial could be a chance finding. It could also be that the study patients with high expectations of acupuncture treatment reported positively biased data. However, the validity of our results is supported by the consistency of findings as judged by a variety of instruments including a headache diary and validated questionnaires on quality of life, disability, and emotional aspects of pain.

The sham acupuncture intervention in our study was designed to minimize potential physiological effects by needling superficially at points distant from the segments of "true" treatment points and by using fewer needles than in the acupuncture group. However, we cannot rule out that this intervention may have had some physiological effects. The nonspecific physiological effects of needling may include local alteration in circulation and immune function as well as neurophysiological and neurochemical responses.[20,21] The question investigated in our comparison of acupuncture and sham acupuncture was not whether skin penetration matters but whether adherence to the traditional concepts of acupuncture makes a difference. For this purpose, our minimal acupuncture intervention was clearly an appropriate sham control although it might not be an inert placebo.

Another explanation for the improvements that we observed could be that acupuncture and sham acupuncture are associated with particularly potent placebo effects. There is some evidence that complex medical interventions or medical devices have higher placebo effects than medication.[22] Furthermore, acupuncture treatment has characteristics that are considered relevant in the context of placebo effects,[23,24] including exotic conceptual framework, emphasis on the "individual as a whole," frequent patient-practitioner contacts, and the repeated "ritual" of needling.

A recent large, pragmatic trial from the United Kingdom has shown that patients receiving acupuncture for chronic headache in addition to care from a generalist physician did significantly better than patients receiving care from generalist physician alone at little additional cost.[25,26] Preliminary results of a large, clinical trial from Germany seem to confirm these findings.[27] However, these studies did not include a sham control group. Given the uncertainties regarding the potential physiological effects of sham interventions and the question of enhanced placebo effects, it is crucial that direct head-to-head comparisons of acupuncture and proven standard drug treatments are conducted in addition to sham-controlled trials. Until now, only 2 rigorous trials have been published that compared acupuncture with metoprolol[28] or flunarizine.[29] Their results suggest that acupuncture might be similarly as effective as medication. Two other trials with head-to-head comparisons of acupuncture and standard drug treatment are currently under way.[30,31] Such trials are also desirable to assess the aspects of safety and compliance. In our study, only minor adverse effects were reported and no patient withdrew due to adverse effects. This com-

pares favorably to findings in trials studying drug treatment. In the largest published randomized trial on migraine prevention, the drop-out rate due to adverse effects was 6.7% for 160 mg of propranolol, 6.9% for 10 mg of flunarizine, and 8.0% for 5 mg of flunarizine.[19] A recent large randomized trial of topiramate reported a drop-out rate of more than 20%.[20]

In conclusion, in our trial, acupuncture was associated with a reduction of migraine headaches compared with no treatment; however, the effects were similar to those observed with sham acupuncture and may be due to nonspecific physiological effects of needling, to a powerful placebo effect, or to a combination of both.

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Study concept and design: Linde, Streng, Jürgens, Brinkhaus, Witt, Wagenpfeil, Pfaffenrath, Hammes, Weidenhammer, Willich, Melchart.
Acquisition of data: Linde, Streng, Jürgens, Hoppe, Wagenpfeil.
Analysis and interpretation of data: Linde, Brinkhaus, Witt, Wagenpfeil, Weidenhammer, Willich, Melchart
Drafting of the manuscript: Linde.
Critical revision of the manuscript for important intellectual content: Linde, Jürgens, Hoppe, Brinkhaus, Witt, Pfaffenrath, Hammes, Weidenhammer, Willich, Melchart.
Statistical analysis: Linde, Streng, Wagenpfeil, Weidenhammer.
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Study supervision: Streng, Wagenpfeil, Pfaffenrath, Willich, Melchart.
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