Annals of Internal Medicine | ARTICLE

Acupuncture and Knee Osteoarthritis

A Three-Armed Randomized Trial

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Background: Despite the popularity of acupuncture, evidence of its efficacy for reducing pain remains equivocal.

Objective: To assess the efficacy and safety of traditional Chinese acupuncture (TCA) compared with sham acupuncture (needling at defined nonacupuncture points) and conservative therapy in patients with chronic pain due to osteoarthritis of the knee.

Design: Randomized, controlled trial.

Setting: 315 primary care practices staffed by 320 practitioners with at least 2 years' experience in acupuncture.

Patients: 1007 patients who had had chronic pain for at least 6 months due to osteoarthritis of the knee (American College of Rheumatology [ACR] criteria and Kellgren–Lawrence score of 2 or 3).

Interventions: Up to 6 physiotherapy sessions and as-needed anti-inflammatory drugs plus 10 sessions of TCA, 10 sessions of sham acupuncture, or 10 physician visits within 6 weeks. Patients could request up to 5 additional sessions or visits if the initial treatment was viewed as being partially successful.

Measurements: Success rate, as defined by at least 36% improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at 26 weeks. Additional end points were WOMAC score and global patient assessment.

Results: Success rates were 53.1% for TCA, 51.0% for sham acupuncture, and 29.1% for conservative therapy. Acupuncture groups had higher success rates than conservative therapy groups (relative risk for TCA compared with conservative therapy, 1.75 [95% CI, 1.43 to 2.13]; relative risk for sham acupuncture compared with conservative therapy, 1.73 [CI, 1.42 to 2.11]). There was no difference between TCA and sham acupuncture (relative risk, 1.01 [CI, 0.87 to 1.17]).

Limitations: There was no blinding between acupuncture and traditional therapy and no monitoring of acupuncture compliance with study protocol. In general, practitioner–patient contacts were less intense in the conservative therapy group than in the TCA and sham acupuncture groups.

Conclusions: Compared with physiotherapy and as-needed anti-inflammatory drugs, addition of either TCA or sham acupuncture led to greater improvement in WOMAC score at 26 weeks. No statistically significant difference was observed between TCA and sham acupuncture, suggesting that the observed differences could be due to placebo effects, differences in intensity of provider contact, or a physiologic effect of needling regardless of whether it is done according to TCA principles.

Ann Intern Med. 2006;145:12-20. www.annals.org
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Central Registration No. ISRCTN27450856.

Osteoarthritis of the knee is an important factor in health care cost in industrialized societies. In Germany, costs directly attributable to osteoarthritis were estimated to be approximately 5.4 billion Euro in 1995 (1, 2). Because there is no cure for osteoarthritis, most guidelines recommend a multimodal pharmacologic and nonpharmacologic approach until total knee replacement is indicated (3, 4). Pharmacologic treatment generally consists of nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors and nonopioid analgesics. Treatment is usually combined with patient education, social support, and physiotherapy. However, even this multimodal approach is often ineffective or has only short-term effects. The probability of adverse events increases with the duration of pharmacologic treatment.

At the 1997 National Institutes of Health Consensus Conference on acupuncture (5), acupuncture was proposed as an option for reducing the dose of or avoiding the use of medication. However, the paucity of scientific evidence called for additional well-designed clinical trials. In a systematic review, 4 of 7 trials conducted in a total of 393 patients with knee osteoarthritis showed statistically significant effects of acupuncture compared with conservative therapy alone or sham acupuncture (6). However, most of the trials were poorly designed, none included long-term follow-up of more than 3 months, sample sizes were often too small, and there were relevant losses to follow-up or raters were not blinded.

To determine whether to reimburse patients for the costs of acupuncture, German social health care insurance organizations initiated the German acupuncture clinical trials (www.gerac.de). An independent consortium of 4 German universities was invited to investigate the efficacy and safety of traditional Chinese acupuncture (TCA) versus sham acupuncture and standardized multimodal therapy for several indications, including osteoarthritis of the knee (7).

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The aim of our study was to compare long-term efficacy and safety (over 26 weeks) of standardized TCA; standardized minimal-depth acupuncture at nonacupuncture points (sham acupuncture) applied in addition to physiotherapy and as-needed anti-inflammatory drugs; and conservative therapy, including anti-inflammatory drugs and physiotherapy, for pain caused by osteoarthritis of the knee. We chose these treatments to investigate a general effect (if any) of the acupuncture needling procedures (acupunctures vs. conservative therapy) and a specific effect (if any) of the localization, stimulation, or depth of needling (TCA vs. sham acupuncture).

Context

The evidence regarding acupuncture for treating osteoarthritis of the knee has been inconclusive.

Contribution

A total of 320 primary care practitioners and 1007 patients with osteoarthritis of the knee participated in this 26-week randomized trial. The proportion of patients achieving the primary end point (>36% improvement on a standardized measure of pain and function) was 53.1% for traditional Chinese acupuncture, 51.0% for sham acupuncture (blinded comparison), and 29.1% for medical treatment (nonblinded comparisons).

Cautions

All groups did not receive an appropriate placebo intervention.

Implications

Acupuncture (traditional or sham) was more effective than medical management alone. Needling alone, even in nontraditional insertion sites; more intensive medical attention; or placebo effects may be responsible for this result.

—The Editors

METHODS

Participants

A total of 1039 eligible patients were enrolled in the study between April 2002 and March 2004. The 320 physicians were selected from a group of experienced primary care practitioners participating in a large cohort study on acupuncture (www.gerac.de). The ethics committees of the University of Heidelberg and the University of Mannheim and all involved local ethics committees approved the study. The study protocol was consistent with the principles of the Declaration of Helsinki.

The inclusion criteria were signed declaration of consent; age 40 years and older; chronic pain in the knee joint for the last 6 months, according to American College of Rheumatology (ACR) criteria (8); radiologic confirmation of osteoarthritis in 1 or both knees (Kellgren–Lawrence score 2 or 3 [9]); Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (10, 11) score of at least 3 points; and a chronic pain score of at least 1, according to the criteria of von Korff and colleagues (12). Patients with other diseases affecting the knee, neurologic and psychiatric diseases, severe coagulopathy, pregnancy, or previous acupuncture treatment for osteoarthritis of the knee were excluded. A detailed list of eligibility criteria was reported by Streitberger and colleagues (13).

The physicians checked the patients' eligibility criteria during a screening examination. A screening telephone interview was done to record baseline WOMAC values, quality of life (12-item Short-Form Health Survey [SF-12]) (14), von Korff scores (15), and use of analgesics. Finally, patients were randomly assigned into 3 treatment groups.

Interventions

Conservative therapy involved 10 visits to practitioners with consultation and a prescription for diclofenac, up to 150 mg/d, or rofecoxib, 25 mg/d, as needed until week 23. The protocol permitted 5 additional visits in weeks 7 to 13 if patients were graded as having a "partially successful" result (10% to 50% reduction in pain after 6 weeks based on the von Korff pain intensity scale) during a telephone interview. If a patient fulfilled the criterion for additional visits, the interviewer informed the patient during the interview and informed the related investigator by fax. The patient could choose whether to participate in the 5 additional visits.

In the TCA and sham acupuncture groups, 10 acupuncture sessions administered over a 6-week period began 2 weeks after screening. Patients receiving acupuncture who met the criterion for partial success were also entitled to 5 additional treatment sessions.

The defined TCA program followed recommendations for optimized acupuncture treatment in clinical studies (16). According to the traditional Chinese theory of the Bi syndrome to treat knee pain, the most important local acupuncture points were included as obligatory points (17–19). In addition, according to traditional Chinese diagnosis (including meridian theory and the most common syndrome differentiation of qi stagnation, kidney deficiency, and dampness and cold), 2 of 16 defined acupuncture points could be chosen. A maximum of 4 Ahshi points was also allowed (**Table 1**).

Sham acupuncture was standardized as minimal-depth needling without stimulation at 10 points at defined distances from TCA points. One point was between the gallbladder and stomach meridian on the distal part of the fibula, 2 cun above the malleolus lateralis toward the knee (cun is a patient-related measure that is the width of a thumb, approximately 1.5 cm, and is used in TCM). Two points were 2 cun and 6 cun, respectively, above the malleolus medialis in the center of the tibia surface area, intracutaneous, without periosteum contact and in the direction of the knee. One point was in the center of the thigh on the connecting line from the center of the patella to the

Table 1. **Components of Study Interventions as Defined in the Study Protocol***

Variable	Traditional Chinese Acupuncture Group	Sham Acupuncture Group	Conservative Therapy Group
Sessions or visits, *n*	10 (+5)†	10 (+5)†	10 (+5)†
Physiotherapy sessions, *n*	6	6	6
Needle location			
Obligatory	Unilateral: ST34, ST36, Xiyan, SP9, SP10, GB34	Bilateral, no proximity to traditional acupoints: 3 at the lower limb, 1 at the upper limb, and 1 at the arm	No acupuncture
Optional	Unilateral: 1–4 Ahshi points; bilateral according to Traditional Chinese Medicine: 1–2 of 16 defined distant points	–	No acupuncture
Needles, *n*	7–15	10	0
Needle diameter, *mm*	0.3	0.3	–
Depth of insertion, *cm*	0.5–3.5 until deqi	Up to 0.5 without deqi	–
Stimulation	Twice	None	–
Duration of needling, *min*	20–30	20–30	–
Allowed medication‡			
Weeks 1 and 2	Diclofenac, 150 mg/d§	Diclofenac, 150 mg/d§	Diclofenac, 150 mg/d, or rofecoxib, 25 mg/d
Weeks 3–23	Diclofenac, 150 mg/d, but only 1 g§	Diclofenac, 150 mg/d, but only 1 g total§	Diclofenac, 150 mg/d, or rofecoxib, 25 mg/d
Weeks 24–26	None	None	None

* Dashes indicate "None."
† "+5" indicates 5 additional sessions or visits if treatment was graded as partially successful after 6 weeks.
‡ In the case of more intensive use of allowed medications, the patient was considered as having treatment failure in ancillary analyses.
§ Rescue medication when acupuncture failed to prevent pain.

anterior superior iliac spine, in the direction of the hip. One point was on the highest spot of the tightened musculus biceps brachii. This control technique was chosen to minimize any supposed nonspecific antinociceptive physiologic effects of deep needling and strong stimulation, including the typical acupuncture sensation of deqi. Noninvasive sham devices, such as the placebo needle (20), were not used. The protocol prescribed the same general procedure, diagnostics, and communication with patients in the TCA and sham acupuncture groups.

The same types of acupuncture needles were used for TCA and sham acupuncture, and all investigators were trained in both techniques. Both knees were treated if affected. When acupuncture did not reduce the pain to a level the patient found acceptable, patients could take up to 150 mg of diclofenac per day during the first 2 treatment weeks and up to a total of 1 g until week 23.

Each of the 3 treatment groups had up to 6 physiotherapy sessions. Corticosteroids and other analgesics besides diclofenac and rofecoxib were explicitly excluded for all patients. Injections, infiltrations, moxibustion, cupping, and electroacupuncture were also prohibited. Additional details are shown in **Table 1** and in the protocol published by Streitberger and colleagues (13).

The patients knew whether they were in the conservative therapy group but were blinded to TCA versus sham acupuncture. The investigators were not blinded to treatment group, but the person doing the telephone interviews for end point measurement was blinded to treatment assignment.

Randomization

The 1:1:1 block randomization with block size of 6, stratified by center, was computer-generated by an independent statistician and was transferred to the randomization center. For each eligible patient, the practitioner called the randomization center and was immediately informed by fax of the patient's treatment group.

Outcomes

The effect on pain and function was measured with the WOMAC score (total score and the subscales standardized to 0 to 10). In patients with 2 affected knees, 1 knee was randomly chosen for evaluation during the initial telephone interview. According to the recommendations of the OsteoArthritis Research Society International (21), success rates were calculated according to a change of at least 36% from baseline WOMAC scores at 13 and 26 weeks after the start of treatment (22). Patients with missing data were considered to have had treatment failure.

Blinded central telephone interviews were conducted in weeks 13 and 26 to record the main and secondary outcome measures (SF-12 [14] and global patient assessment [23]). At each visit, the investigator documented adverse events since the last visit, and a medical doctor performed coding using the *Medical Dictionary for Regulatory Activities* (MedDRA).

Statistical Analyses

The sample size calculation assumed a success rate of 60% for TCA (24). The success rates for conservative treatment and sham acupuncture were assumed to be 40% and 50%, respectively. Thirty percent of trial patients were as-

sumed to be nonadherent. The resulting treatment failures reduced the success rate to 28% for conservative treatment, 35% for sham acupuncture, and 42% for TCA. On the basis of this scenario, 294 patients needed to be allocated to each treatment group to establish a difference among the treatments on a 5% level and with a power of 90% (25).

Success rates were analyzed by random-effects logistic regression models. Treatment was coded as a categorical variable with 3 levels, and 35 regional clusters of practitioners were considered as random effects. The use of the random-effects model was predetermined in the protocol to adjust for unexplained heterogeneity related to regional clusters of practitioners. The primary analysis was also adjusted for the number of affected knees (fixed effects, 2 levels). Relative risks and absolute risk differences were calculated for the unadjusted success rates.

The multiple testing problem caused by the comparison of the 3 treatments was handled by a closed test procedure (26, 27) to guarantee the prespecified type I error of 5% for all pairwise comparisons within the same model. The mixed-effects models used the likelihood ratio tests to assess differences among the 3 treatment groups. If the global test rejected the null hypothesis of no difference between all treatments, paired comparisons were performed between treatment groups in a second step, also using likelihood ratio tests. For the primary analyses, an intention-to-treat sample was used, including all randomly assigned patients with at least 1 treatment.

The sensitivity analyses for the success rate studied included adjustment for the additional covariates, baseline WOMAC score, use of physiotherapy, and extension of treatment period. Further analyses looked at interaction effects, such as treatment and baseline WOMAC scores, treatment and number of affected knees, treatment and use of physiotherapy, and treatment and extension of the treatment period. Treatment-induced changes in the WOMAC score and its subscales between the treatment groups at specific time points were studied by using a linear mixed-effects model in which treatment and number of affected knees were considered as fixed and regional cluster was considered as a random effect. We used descriptive analysis to tabulate demographic and baseline characteristics of study participants by randomization group.

The analyses were performed with SAS, version 8.2 (SAS Institute, Inc., Cary, North Carolina). The mixed-effects models were run by using the SAS macro GLIMMIX with the maximum likelihood option.

Role of the Funding Source

A consortium of German social health care insurance organizations (Allgemeine Ortskrankenkassen, Betriebskrankenkassen, Innungskrankenkassen, Bundesknappschaft, Landwirtschaftliche Krankenkassen, and See-Krankenkasse) provided funding for this study at the request of German health authorities. Financial support was given to the Institute of Medical Biometry and Informatics (Uni-

Figure. **Study flow diagram.**

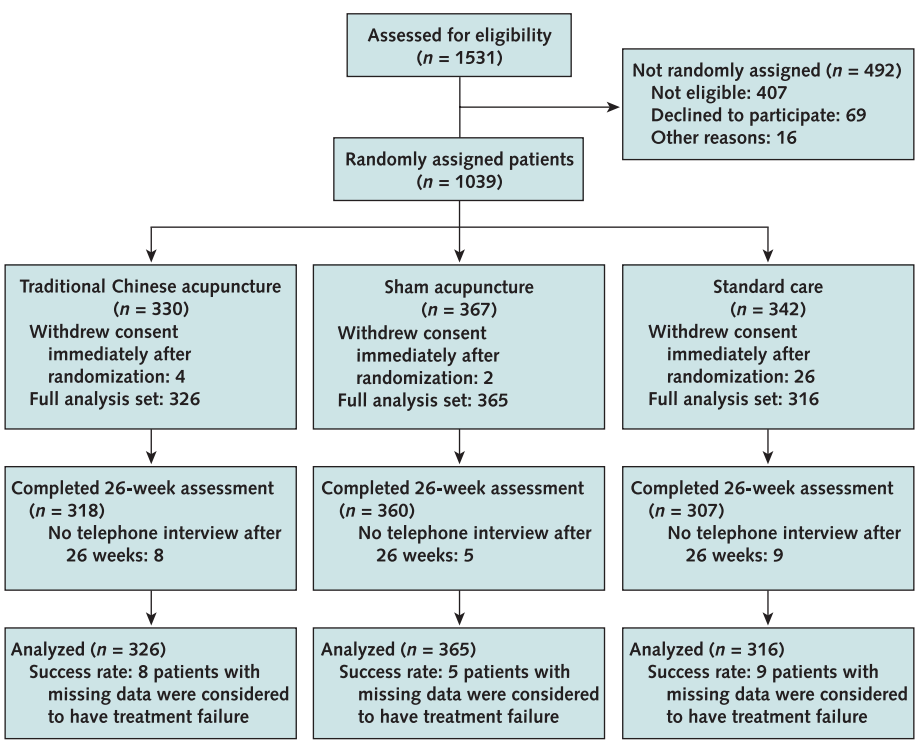

Table 2. **Baseline Characteristics***

Variable	Traditional Chinese Acupuncture Group (*n* = 326)	Sham Acupuncture Group (*n* = 365)	Conservative Therapy Group (*n* = 316)
Women, *n (%)*	220 (67.5) [0]	255 (69.9) [0]	218 (69.0) [0]
Mean age (SD), *y*	62.8 (9.9) [0]	63.0 (10.1) [0]	62.6 (10.1) [0]
Mean body mass index (SD), kg/m^2	29.6 (4.8) [4]	29.4 (4.8) [2]	29.8 (5.1) [1]
Affected knees	[5]	[4]	[7]
1, *n (%)*	221 (68.8)	248 (68.7)	204 (66.0)
2, *n (%)*	100 (31.2)	113 (31.3)	105 (34.0)
Mean duration of pain (SD), *mo*	65.6 (76.0)	62 (63.6)	68.1 (73.8)
Kellgren score	[1]	[1]	[4]
0–1, *n (%)*	1 (0.3)	3 (0.8)	0 (0.0)
2, *n (%)*	211 (64.9)	237 (65.1)	182 (58.3)
3, *n (%)*	112 (34.5)	124 (34.1)	130 (41.7)
4, *n (%)*	1 (0.3)	0 (0.0)	0 (0.0)
Previous medication in the past month			
Oral, *n (%)*	102 (31.3)	96 (26.3)	103 (32.6)
Ointment, *n (%)*	40 (12.3)	41 (11.2)	40 (12.7)
Oral and ointment, *n (%)*	48 (14.7)	55 (15.1)	30 (9.5)
No medication, *n (%)*	136 (41.7)	173 (47.4)	141 (44.6)

* Data in square brackets are numbers of missing observations. Two of the patients in the conservative treatment group had received previous intravenous medication.

versity of Heidelberg); the Department of Medical Informatics, Biometry and Epidemiology (University of Bochum); and the BG-Clinic Bergmannsheil (University of Bochum). The insurance organizations did not participate in the design, analysis, or reporting of the study.

RESULTS

Recruitment

Of 1531 screened patients, 492 could not be included in the study, mainly because they did not meet all eligibility criteria (**Figure**). Thus, 1039 patients were randomly assigned into 3 treatment groups by 297 investigators. Thirty-two patients declined further participation immediately after randomization and were excluded from the analysis because no measurements were available (28). Therefore, 1007 patients were analyzed following intention-to-treat principles: 326 randomly assigned to TCA (32.4%), 365 randomly assigned to sham acupuncture (36.2%), and 316 randomly assigned to conservative therapy (31.4%). Interviews of 985 patients were available after 26 weeks (22 patients were lost to follow-up). The per-protocol analysis set consists of 611 patients: 200 who received TCA (32.7%), 223 who received sham acupuncture (36.5%), and 188 who received conservative therapy (30.8%).

Baseline Data

Baseline data of 1007 patients before randomization are presented in **Table 2**. Most study patients were women (68.8%). Twenty-five percent of the patients were younger than age 55 years. There were no pretreatment differences among the 3 treatment groups with respect to demographic characteristics, outcome variables (**Table 3**), disease-specific characteristics, and medication use, suggesting that the randomization procedure produced comparable groups at baseline.

Interventions

Adherence to the planned interventions is shown in **Appendix Table 1** (available at www.annals.org). All acupuncture treatments for a given patient were completed by the same physician. Patients in the acupuncture groups received treatment at each visit. The mean number of acupuncture sessions was 12.5 in the TCA and sham groups. Patients in the conservative therapy group had a mean of 8.4 visits. A total of 124 (38.0%) patients in the TCA group, 141 (38.6%) in the sham group, and 197 (62.3%) in the conservative therapy group had physiotherapy. The use of analgesics was documented during the telephone interviews. In the 4-week period before the start of the study, the percentage of patients not using analgesics was homogeneously distributed over the 3 treatment groups: 176 patients in the TCA group (54.0%), 214 in the sham acupuncture group (58.6%), and 183 in the conservative therapy group (57.9%). Patients taking no analgesics during the trial differed by treatment group: 162 in the TCA group (50.3%), 202 in the sham acupuncture group (55.8%), and 104 in the conservative therapy group (33.2%). Twenty patients took rofecoxib during the trial, 5 each in the TCA and sham acupuncture groups and 10 in the conservative therapy group.

Primary End Point

The observed success rates were 53.1% for the TCA group, 51.0% for the sham acupuncture group, and 29.1% for the conservative therapy group (**Table 3**). The observed success rates adjusted for regional cluster and number of affected knees were 55.3%, 53.2%, and 31.1%, respectively.

Random-effects multivariate logistic regression analysis confirmed the existence of strong overall differences among treatment groups ($P < 0.001$ for global comparison). Pair-

wise comparisons showed statistically significantly increased success rates in the TCA and sham acupuncture groups compared with the conservative therapy group ($P < 0.001$ for both comparisons) and no difference between the TCA and sham acupuncture groups ($P = 0.48$). The relative risks and the absolute risk differences, respectively, for the unadjusted success rates were 1.75 (95% CI, 1.43 to 2.13) and 24.0% (CI, 16.6% to 31.3%) for TCA versus conservative therapy, 1.73 (CI, 1.42 to 2.11) and 21.8% (CI, 14.7% to 29.0%) for sham acupuncture versus conservative therapy, and 1.01 (CI, 0.87 to 1.17) and 2.1% (CI, −5.4% to 9.6%) for TCA versus sham acupuncture.

Secondary End Points

Table 3 shows statistically significant changes with respect to total WOMAC score. The changes in the TCA and sham acupuncture groups were much more distinct than those measured in the conservative therapy group (−2.3 [CI, −2.5 to −2.0], −2.1 [CI, −2.3 to −1.8], and −1.2 [CI, −1.5 to −0.9], respectively). Results were comparable at week 13.

The dichotomized global patient assessment showed statistically significant differences among treatment groups ($P < 0.001$ for global comparison), with a higher rate of satisfaction in the TCA and sham acupuncture groups at week 26 (73.0% for the TCA group, 62.5% for the sham acupuncture group, and 47.1% for the conservative therapy group). Similar results were observed at week 13. The SF-12 physical subscale at week 26 was also greater with TCA and sham acupuncture than with conservative therapy. Differences in the SF-12 mental subscale could not be detected among the treatment groups (**Table 3**). Results for WOMAC subscores are shown in **Appendix Table 2** (available at www.annals.org).

Ancillary Analyses

The same pattern of differences was present in per-protocol and in all other sensitivity analyses (**Appendix Table 3**, available at www.annals.org). **Appendix Table 3** also shows outcome data assuming that postrandomization events, such as "use of too much medication," "use of prohibited treatments," and "change of treatment group," indicated treatment failure. Redefinition of the primary end point using these events did not alter the general conclusions. Including a term for interaction between treatment group and treatment extension, baseline WOMAC, or number of affected knees in our mixed-effects models for the primary end point did not affect the model fit or the statistical significance of the group differences. Including a term for interaction between physiotherapy and treatment group in the same models did affect model fit but did not

Table 3. **Primary and Secondary Outcomes, Differences between Groups, and Changes over Time***

Variable	Traditional Chinese Acupuncture Group ($n = 326$)	Sham Acupuncture Group ($n = 365$)	Conservative Therapy Group ($n = 316$)	Traditional Chinese Acupuncture versus Conservative Therapy	Sham Acupuncture versus Conservative Therapy	Traditional Chinese Acupuncture versus Sham Acupuncture
Success rate, *n (%)*						
Week 13	168 (51.5)	179 (49.0)	85 (26.9)	$P < 0.001$	$P < 0.001$	$P = 0.51$
Week 26	173 (53.1)	186 (51.0)	92 (29.1)	$P < 0.001$	$P < 0.001$	$P = 0.48$
Total WOMAC score†						
Mean baseline score ± SE	5.4 ± 0.20 [0]	5.5 ± 0.19 [0]	5.5 ± 0.20 [1]	–	–	–
Mean change from baseline at week 13 (95% CI)	−2.1 (−2.4 to −1.9) [12]	−1.9 (−2.2 to −1.7) [7]	−0.9 (−1.2 to −0.7) [8]	−1.2 (−1.5 to −0.9)	−1.0 (−1.3 to −0.7)	0.2 (−0.1 to 0.5)
Mean change from baseline at week 26 (95% CI)	−2.3 (−2.5 to −2.0) [8]	−2.1 (−2.3 to −1.8) [5]	−1.2 (−1.5 to −0.9) [10]	−1.1 (−1.4 to −0.8)	−0.9 (−1.2 to −0.6)	0.2 (−0.1 to 0.5)
SF-12 physical subscale						
Mean baseline score ± SE	30.5 ± 0.87 [4]	30.7 ± 0.82 [0]	30.2 ± 0.89 [6]	–	–	–
Mean change from baseline at week 13 (95% CI)	6.4 (4.3 to 8.5) [17]	5.2 (4.2 to 6.2) [7]	3.0 (1.9 to 3.7) [14]	$P < 0.001$	$P = 0.003$	$P = 0.06$
Mean change from baseline at week 26 (95% CI)	7.0 (5.9 to 8.1) [15]	5.9 (4.9 to 6.9) [8]	3.5 (2.5 to 4.5) [17]	$P < 0.001$	$P < 0.001$	$P = 0.11$
SF-12 mental subscale						
Mean baseline score ± SE	48.9 ± 1.58 [4]	48.9 ± 1.52 [0]	50.4 ± 1.63 [6]	–	–	–
Mean change from baseline at week 13 (95% CI)	2.1 (0.9 to 3.3) [17]	3.0 (2.1 to 4.5) [7]	0.8 (−0.4 to 2.0) [14]	$P = 0.38$	$P = 0.06$	$P = 0.32$
Mean change from baseline at week 26 (95% CI)	1.6 (0.4 to 2.8) [15]	3.1 (1.9 to 4.3) [8]	1.3 (0.1 to 2.5) [17]	$P = 0.96$	$P = 0.36$	$P = 0.14$
Global patient assessment, *n (%)*						
Week 13	220 (70.1) [12]	228 (63.9) [8]	143 (46.6) [9]	$P < 0.001$	$P < 0.001$	$P = 0.09$
Week 26	233 (73.0) [7]	225 (62.5) [5]	144 (47.1) [10]	$P < 0.001$	$P < 0.001$	$P = 0.004$

* Calculations and *P* values are based on a linear mixed-effects model (adjusted for number of affected knees and regional cluster). Data in square brackets are numbers of missing observations. The WOMAC subscale results and von Korff classification are shown in Appendix Table 2 (available at www.annals.org). SF-12 = 12-item Short-Form Health Survey; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† A scale of 0 to 10 was used for the WOMAC score.

Table 4. **Adverse Events and the 5 Most Frequent Events Reported in Each Group***

Variable	Traditional Chinese Acupuncture Group (*n* = 326)	Sham Acupuncture Group (*n* = 365)	Conservative Therapy Group (*n* = 316)
Observed adverse events, *n (%)*	179 (100)	177 (100)	159 (100)
5 most frequent preferred terms, *n (%)*			
Arthralgia	16 (8.9)	15 (8.5)	13 (8.2)
Bone pain	10 (5.6)	10 (5.6)	13 (8.2)
Hematoma	12 (6.7)	18 (10.2)	1 (0.6)
Back pain	8 (4.5)	11 (6.2)	6 (3.8)
Joint lock	9 (5.0)	8 (4.5)	5 (3.1)

* Preferred terms are from the *Medical Dictionary for Regulatory Activities* coding system. Appendix Table 6 (available at www.annals.org) shows detailed information on adverse events.

affect the statistical significance of the group differences. **Appendix Table 4** (available at www.annals.org) shows detailed results of the multivariate analyses.

Blinding

The quality of blinding between the TCA and sham acupuncture groups was assessed in the final interview. Only 33 patients (16 in the TCA group and 17 in the sham acupuncture group) stated that they had been unblinded by the treating physician. Almost half (n = 330 [49%]) of 675 patients with TCA or sham acupuncture were unaware of which treatment they received. Data on this variable were missing in 16 patients. Of the 345 patients who said they knew their treatment, 154 (45%) guessed incorrectly. The 33 patients who were unblinded by the treating physician are among the 345 patients increasing the rate of correct presumptions. Therefore, the estimates were roughly random, and blinding between the TCA and sham acupuncture groups was successful (**Appendix Table 5**, available at www.annals.org).

Safety

Numbers of adverse events were comparable for the 3 groups. One hundred seventy-nine adverse events were recorded in the TCA group, 177 were recorded in the sham group, and 159 were recorded in the conservative therapy group. A total of 285 patients had at least 1 adverse event (91 in the TCA group, 97 in the sham acupuncture group, and 97 in the conservative therapy group). Fifty serious adverse events were reported (23 in 20 patients in the TCA group, 9 in 9 patients in the sham acupuncture group, and 18 in 16 patients in the conservative therapy group). Hematoma was reported more often in the TCA and sham acupuncture groups than in the conservative therapy group (**Table 4**; **Appendix Table 6**, available at www.annals.org). The most frequent adverse events were musculoskeletal disorders. One 83-year-old woman in the TCA group died of a myocardial infarction during the study. The investigator saw no causal relationship between her death and the treatment. The medication record showed that this patient regularly took rofecoxib, 25 to 50 mg/d, 4 weeks before and during the study. Other notable serious adverse events were syncope and stroke in 1 patient each in the TCA group; myocardial infarction in 1 patient in the sham acupuncture group; and renal failure, melena, and deep venous thrombosis in 1 patient each in the conservative therapy group.

Concomitant Treatments

A broad variety of concomitant treatments were documented in all 3 groups, but only 55 patients (10 in the TCA group [3.1%], 11 in the sham acupuncture group [3.0%], and 34 in the conservative therapy group [10.4%]) received treatment prohibited by the protocol, such as local injections, acupressure, or local physical therapy. Concomitant treatment was the reason for assuming treatment failure in 162 patients (60 in the TCA group [18.4%], 47 in the sham acupuncture group [12.9%], and 55 in the conservative therapy group [17.4%]) in the ancillary analyses that modified the definition of success rate on the basis of postrandomization events (**Appendix Table 3**, available at www.annals.org).

DISCUSSION

This study shows that both TCA and sham acupuncture improve pain and functionality in patients with osteoarthritis of the knee more than conservative therapy. The effect was assessed by success rates based on the WOMAC scores. Surprisingly, no differences were observed between the TCA and sham acupuncture groups. Superiority of TCA and sham acupuncture over conservative therapy and no detectable difference between TCA and sham acupuncture also held true for all secondary end points. Additional sensitivity analyses with adjustment for potential influencing factors support these findings. Apart from hematomas, no obvious adverse effects due to acupuncture were detected. This supports known statements about the safety of acupuncture (29). To our knowledge, our study is the largest reported randomized, controlled trial on the efficacy and safety of acupuncture in patients with symptomatic osteoarthritis of the knee and moderate to severe chronic pain. Blinding between TCA and sham acupuncture was successful, the number of patients who left the study was kept low, and homogeneous treatment groups could be created with respect to demographic characteristics and

baseline values. However, our study has several limitations. Adherence to the predefined acupuncture schemes could not be monitored. The recruited patients assumedly had an interest in acupuncture, possibly introducing a selection effect.

We interpret the observed superiority of TCA and sham acupuncture over conservative therapy as evidence of an improved outcome in patients with osteoarthritis of the knee when acupuncture is used as an adjunct to conservative therapy. However, because complete blinding was impossible, this study does not allow us to determine whether the observed effectiveness of TCA and sham acupuncture was due to placebo effects, intensity of provider contact, or a physiologic effect of needling.

An effect of needle insertion (deep or minimal), more intensive practitioner–patient contact (placebo effect of a "healing ritual" [30]), or patients' expectations (a "meaning response," according to Moerman and Jonas [31]) may explain our observations. The absence of a specific effect of TCA is surprising: Specificity of needling points, depth of needling with stimulation, and deqi sensation do not result in marked effects. The TCA scheme used in our study was based on different acupuncture schools. We cannot be completely sure, however, that there are no active points outside our TCA scheme and that no active point was included in our sham acupuncture scheme. Our observation raises the question of whether there is a single optimal point selection and whether deep needling with stimulation and deqi sensation is superior to shallow needling.

Two randomized, controlled trials using TCA and sham acupuncture in patients with osteoarthritis of the knee (32, 33) reported results similar to those of our study. They also established superiority of TCA and sham acupuncture over some control therapies but—contrary to our study—reported superiority of TCA over sham acupuncture. These contradictory results may be attributable to differences in study design, outcome measures, and acupuncture schemes. Witt and colleagues (32) considered the reduction in WOMAC score after 8 weeks (directly at the end of the treatment) as the primary end point. The observed difference between TCA and sham acupuncture was moderate compared with the differences between TCA or sham acupuncture and the control; the difference diminished considerably until week 26. Moreover, the assessment was done by the patients themselves using questionnaires instead of by blinded telephone interviewers as in our study. Despite a similar basic concept of sham acupuncture and TCA, differences in the choice of acupuncture points might have influenced the results. Sham acupuncture might have been less effective or TCA, including ear acupuncture, might have been more effective than in our study. Berman and colleagues (33) compared TCA plus electrostimulation at 1 point with a sham procedure different from our scheme, both applied in addition to conservative therapy (needle insertion at only 2 nonacupuncture points combined with noninvasive mock needle placement at acupuncture points). The setting was different from that in our trial; 2 outpatient clinics recruited all patients. Main end points were the WOMAC pain and function scores at week 8. Another recent study (34) compared acupuncture with electrostimulation versus placebo acupuncture (without needle insertion). The superiority of acupuncture in this trial together with our results could indicate that needling alone contributes to the efficacy of acupuncture.

Studies of nonsteroidal anti-inflammatory drugs usually report higher success rates than that seen in our study for conservative therapy. A possible explanation is the stringent long-term primary end point in our study compared with studies including a drug regimen and placebo, in which the effect is usually measured immediately after a well-specified short-term treatment period.

We believe that our findings support the role of acupuncture in the multimodal treatment of patients with pain and functional limitations due to osteoarthritis of the knee, even if the mechanisms of its effects remain unclear. Acupuncture could improve conservative therapy and reduce the use of analgesics. Further investigation is necessary to determine whether the mechanism of the observed effect of acupuncture is due to physiologic effects of needling, intensity of provider contact, or placebo effects.

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Acknowledgments: The authors thank Albrecht Molsberger, MD, for supporting the development of the acupuncture schemes and Christina Klose for data management.

Potential Financial Conflicts of Interest: *Grants received:* C. Maier, H.-J. Trampisch, N. Victor (Consortium of Allgemeine Ortskrankenkassen, Betriebskrankenkassen, Innungskrankenkassen, Bundesknappschaft, Landwirtschaftliche Krankenkassen, and See-Krankenkassen).

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Appendix Table 1. **Received Interventions***

Variable	Traditional Chinese Acupuncture Group (*n* = 326)	Sham Acupuncture Group (*n* = 365)	Conservative Therapy Group (*n* = 316)
Received treatment, *n*			
Traditional Chinese acupuncture	326	7	8
Sham acupuncture	0	358	1
Conservative therapy	0	0	307
Mean treatment visits in weeks 1–13 (SD), *n*	12.5 (2.7)†	12.5 (2.6)†	8.4 (4.4)
Median treatment visits, *n*	15	15	10
Suitable for treatment extensions weeks 7–13), *n (%)*	196 (60.1)	203 (55.6)	121 (38.3)
Received treatment extensions (weeks 7–13), *n (%)*	178 (54.6)	196 (53.7)	104 (32.9)
Physiotherapy			
Patients with at least 1 physiotherapy session, *n (%)*	124 (38.0)	141 (38.6)	197 (62.3)
Mean physiotherapy sessions (SD), *n*	8.7 (6.2)	8.8 (7.7)	11 (6.8)
Median physiotherapy sessions, *n*	6	6	10
Patients who took at least 1 NSAID, *n (%)*‡			
Week 1 and 2	78 (24.1)	85 (23.7)	132 (42.7)
Weeks 3–23	133 (42.5)	132 (37.4)	179 (59.1)
Weeks 24–26	61 (19.1)	80 (22.2)	114 (37.1)
Patients who did not take analgesics during the study, *n (%)*	162 (49.7)	202 (55.3)	104 (32.9)
Patients who did not take NSAIDs during the study, *n (%)*	164 (50.3)	204 (55.8)	105 (33.2)

* NSAID = nonsteroidal anti-inflammatory drug.
† Equal to the number of acupuncture sessions.
‡ Treatment was administered without gels or creams. Percentages are based on all patients who participated in the corresponding telephone interview.

Appendix Table 2. **Western Ontario and McMaster Universities Osteoarthritis Index Subscores and von Korff Classification by Group over Time***

Variable	Baseline	13 Weeks	26 Weeks
WOMAC pain subscore†			
TCA group	5.3 (5.04 to 5.46) [0]	3.0 (2.77 to 3.28) [11]	2.9 (2.65 to 3.17) [8]
Sham acupuncture group	5.3 (5.12 to 5.53) [0]	3.3 (3.06 to 3.55) [7]	3.2 (2.93 to 3.43) [5]
Conservative therapy group	5.2 (4.93 to 5.36) [1]	4.3 (4.04 to 4.56) [7]	4.0 (3.69 to 4.22) [9]
Difference between TCA and conservative therapy	0.1 (−0.14 to 0.37)	−1.3 (−1.60 to −0.93)	−1.0 (−1.38 to −0.71)
Difference between sham acupuncture and conservative therapy	0.2 (−0.08 to 0.42)	−1.0 (−1.31 to −0.67)	−0.8 (−1.10 to −0.45)
Difference between sham acupuncture and TCA	0.1 (−0.19 to 0.31)	0.3 (−0.05 to 0.60)	0.3 (−0.05 to 0.59)
P value	0.41‡	<0.001‡	<0.001‡
WOMAC stiffness subscore†			
TCA group	5.6 (5.39 to 5.90) [0]	3.5 (3.19 to 3.76) [11]	3.3 (3.02 to 3.59) [8]
Sham acupuncture group	5.7 (5.41 to 5.90) [0]	3.7 (3.43 to 3.97) [7]	3.6 (3.29 to 3.83) [5]
Conservative therapy group	5.7 (5.38 to 5.91) [1]	4.6 (4.35 to 4.93) [7]	4.5 (4.16 to 4.74) [9]
Difference between TCA and conservative therapy	−0.0 (−0.32 to 0.31)	−1.2 (−1.53 to −0.79)	−1.1 (−1.51 to −0.76)
Difference between sham acupuncture and conservative therapy	−0.0 (−0.31 to 0.31)	−0.9 (−1.30 to −0.58)	−0.9 (−1.25 to −0.53)
Difference between sham acupuncture and TCA	0.0 (−0.30 to 0.31)	0.2 (−0.14 to 0.58)	0.2 (−0.11 to 0.60)
P value	0.99‡	<0.001‡	<0.001‡
WOMAC functionality subscore†			
TCA group	5.4 (5.23 to 5.64) [0]	3.3 (3.06 to 3.58) [12]	3.2 (2.93 to 3.45) [8]
Sham acupuncture group	5.6 (5.41 to 5.80) [0]	3.7 (3.43 to 3.92) [7]	3.6 (3.30 to 3.80) [5]
Conservative therapy group	5.5 (5.36 to 5.78) [1]	4.7 (4.39 to 4.92) [7]	4.4 (4.11 to 4.64) [9]
Difference between TCA and conservative therapy	−0.1 (−0.38 to 0.11)	−1.3 (−1.67 to −1.00)	−1.2 (−1.52 to −0.83)
Difference between sham acupuncture and conservative therapy	0.0 (−0.23 to 0.25)	−1.0 (−1.31 to −0.66)	−0.8 (−1.16 to −0.49)
Difference between sham acupuncture and TCA	0.1 (−0.09 to 0.39)	0.4 (0.03 to 0.67)	0.3 (0.02 to 0.68)
P value	0.41‡	<0.001‡	<0.001‡
Change in WOMAC pain subscore from baseline†			
TCA group	–	−2.2 (−2.47 to −1.95) [11]	−2.3 (−2.60 to −2.05) [8]
Sham acupuncture group	–	−2.0 (−2.22 to −1.72) [7]	−2.1 (−2.37 to −1.85) [5]
Conservative therapy group	–	−0.8 (−1.11 to −0.58) [8]	−1.2 (−1.46 to −0.90) [10]
Difference between TCA and conservative therapy	–	−1.4 (−1.71 to −1.03)	−1.1 (−1.49 to −0.81)
Difference between sham acupuncture and conservative therapy	–	−1.1 (−1.45 to −0.79)	−0.9 (−1.27 to −0.60)
Difference between sham acupuncture and TCA	–	0.2 (−0.08 to 0.57]	0.2 (−0.11 to 0.54)
P value	–	<0.001‡	<0.001‡
Change in WOMAC stiffness subscore from baseline†			
TCA group	–	−2.1 (−2.45 to −1.83) [11]	−2.3 (−2.61 to −2.00) [8]
Sham acupuncture group	–	−2.0 (−2.24 to −1.66) [7]	−2.1 (−2.38 to −1.79) [5]
Conservative therapy group	–	−1.0 (−1.34 to −0.72) [8]	−1.2 (−1.54 to −0.91) [10]
Difference between TCA and conservative therapy	–	−1.1 (−1.50 to −0.71)	−1.1 (−1.48 to −0.67)
Difference between sham acupuncture and conservative therapy	–	−0.9 (−1.30 to −0.53)	−0.9 (−1.25 to −0.46)
Difference between sham acupuncture and TCA	–	0.2 (−0.19 to 0.57)	0.2 (−0.17 to 0.61)
P value	–	<0.001‡	<0.001‡
Change in WOMAC functionality subscore from baseline†			
TCA group	–	−2.1 (−2.36 to −1.83) [12]	−2.2 (−2.49 to −1.94) [8]
Sham acupuncture group	–	−1.9 (−2.14 to −1.63) [7]	−2.0 (−2.29 to −1.77) [5]
Conservative therapy group	–	−0.9 (−1.18 to −0.64) [8]	−1.2 (−1.47 to −0.91) [10]
Difference between TCA and conservative therapy	–	−1.2 (−1.50 to −0.85)	−1.0 (−1.35 to −0.67)
Difference between sham acupuncture and conservative therapy	–	−1.0 (−1.29 to −0.66)	−0.8 (−1.16 to −0.51)
Difference between sham acupuncture and TCA	–	0.2 (−0.11 to 0.51)	0.2 (−0.15 to 0.50)
P value	–	<0.001‡	<0.001‡
von Korff classification, %			
TCA group	[38]	[59]	[46]
0	0.0	0.7	3.9
1	11.1	47.6	56.8
2	36.8	24.7	15.7
3	31.9	17.6	15.4
4	20.1	9.4	8.2

Continued on following page

Appendix Table 2—Continued

Variable	Baseline	13 Weeks	26 Weeks
Sham acupuncture group	[40]	[57]	[32]
0	0.0	0.0	1.8
1	7.1	43.5	53.8
2	39.4	28.2	23.1
3	30.2	17.9	12.6
4	23.4	10.4	8.7
Conservative therapy group	[34]	[45]	[32]
0	0.0	0.4	1.8
1	10.3	28.0	30.6
2	32.3	32.1	34.5
3	36.2	26.6	21.8
4	21.3	12.9	11.3
P value for TCA vs. conservative therapy	0.62	<0.001	<0.001
P value for sham acupuncture vs. conservative therapy	0.12	0.002	<0.001
P value for sham acupuncture vs. TCA	0.27	0.46	0.10
Overall *P* value	0.27	<0.001	<0.001

* The WOMAC data are presented as the adjusted mean for regional cluster and 1 affected knee (95% CI). Data in square brackets are numbers of missing or not applicable observations. There were 326, 365, and 316 patients in the TCA, sham acupuncture, and conservative therapy groups, respectively. Negative changes in WOMAC score indicate improvement; negative WOMAC changes favor the first group. TCA = traditional Chinese acupuncture; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† A scale of 0 to 10 was used for the WOMAC score.
‡ Likelihood ratio test for the global hypothesis of no differences between groups.

Appendix Table 3. Success Rates after 26 Weeks and Interfering Events by Group and Analysis Population*

Variable	Traditional Chinese Acupuncture Group	Sham Acupuncture Group	Conservative Therapy Group
Patients (full analysis set), *n (%)*	326 (100)	365 (100)	316 (100)
Failure due to <36% improvement in the WOMAC score, *n*	145	174	214
Failure due to missing value, *n*	8	5	10
Success rate after 26 weeks, *n (%)*	173 (53.1)	186 (51.0)	92 (29.1)
Events that may interfere with treatment success, *n*			
Too much medication only	45	35	31
Prohibited treatments only	8	3	12
Change of treatment group only	0	3	5
Events due to too much medication and prohibited treatments	7	7	12
Events due to too much medication and change of treatment group	0	2	0
Success rate after 26 weeks without interfering event, *n (%)*	113 (34.7)	136 (37.3)	32 (10.1)
Patients (per-protocol set), *n (%)*	200 (100)	223 (100)	188 (100)
Failure due to <36% improvement in the WOMAC score, *n*	80	97	133
Success rate after 26 weeks, *n (%)*	120 (60.0)	126 (56.5)	55 (29.3)
Events that may interfere with treatment success, *n*			
Too much medication only	27	22	19
Prohibited treatments only	4	0	4
Events due to too much medication and prohibited treatments	4	1	3
Success rate after 26 weeks without interfering event, *n (%)*	85 (42.5)	103 (46.2)	29 (15.4)

* Treatment success was a ≥36% improvement in the WOMAC score, and treatment failure was <36% improvement in the WOMAC score or missing value. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Appendix Table 4. Detailed Results of Multivariate Random-Effects Logistic Regression Analyses of the Primary End Point*

Variable	Estimate (95% CI)
Odds ratio for model 1: model contains a random intercept for regional cluster and the fixed-effects treatment group and both knees (SD of random effect, 0.147)	
Conservative therapy	0.451 (0.344–0.593)
TCA vs. conservative therapy	2.746 (1.981–3.806)
Sham acupuncture vs. TCA	0.918 (0.680–1.239)
Sham acupuncture vs. conservative therapy	2.520 (1.833–3.466)
Both knees affected	0.742 (0.563–0.979)
Odds ratio for model 2: model 1 extended by covariate baseline WOMAC (SD of random effect, 0.147)	
Conservative therapy	0.278 (0.160–0.483)
TCA vs. conservative therapy	2.748 (1.980–3.814)
Sham acupuncture vs. TCA	0.911 (0.674–1.230)
Sham vs. conservative therapy	2.503 (1.818–3.445)
Both knees affected	0.731 (0.554–0.965)
Baseline WOMAC score	1.093 (1.005–1.189)
Odds ratio for model 3: model 1 extended by covariate patients with physiotherapy (SD of random effect, 0.154)	
Conservative therapy	0.487 (0.354–0.670)
TCA vs. conservative therapy	2.666 (1.912–3.716)
Sham acupuncture vs. TCA	0.918 (0.680–1.239)
Sham acupuncture vs. conservative therapy	2.448 (1.770–3.385)
Both knees affected	0.745 (0.565–0.982)
Patients with physiotherapy	0.882 (0.678–1.147)
Odds ratio for model 4: model 1 extended by covariate treatment extension (SD of random effect, 0.185)	
Conservative therapy	0.329 (0.244–0.444)
TCA vs. conservative therapy	2.355 (1.684–3.294)
Sham acupuncture vs. TCA	0.922 (0.679–1.253)
Sham vs. conservative therapy	2.172 (1.566–3.012)
Both knees affected	0.729 (0.549–0.968)
Treatment extension	2.407 (1.850–3.132)
Odds ratio for model 5: model 1 extended by baseline WOMAC treatment interaction and both knees treatment interaction (SD of random effect, 0.147)	
Conservative therapy	0.400 (0.153–1.047)
TCA vs. conservative therapy	1.366 (0.390–4.785)
Sham acupuncture vs. TCA	1.305 (0.416–4.096)
Sham vs. conservative therapy	1.783 (0.533–5.970)
Both knees affected	0.760 (0.448–1.288)
Baseline WOMAC score	1.022 (0.870–1.200)
TCA vs. conservative therapy (baseline WOMAC score)	1.144 (0.920–1.423)
Sham acupuncture vs. TCA (baseline WOMAC score)	0.927 (0.760–1.130)
TCA vs. conservative therapy (both knees affected)	0.861 (0.422–1.754)
Sham acupuncture vs. TCA (both knees affected)	1.203 (0.626–2.313)

* An odds ratio <1 means success rate below 0.5; an odds ratio >1 favors the first group. Odds ratios are provided to show how parameter estimates were affected by the incorporation of additional model terms. They should be interpreted with caution as relative risks in case of high success rates. Conservative therapy is taken as baseline, and corresponding odds for treatment success are given. TCA = traditional Chinese acupuncture; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Appendix Table 5. Quality of Blinding between the Traditional Chinese Acupuncture and Sham Acupuncture Groups*

Patient's Interview Response	Traditional Chinese Acupuncture Group (n = 333)	Sham Acupuncture Group (n = 358)	Total (n = 691)
Could not guess treatment received, *n*	158	172	330
Did guess treatment received, *n (%)*	165 (100)	180 (100)	345 (100)
Correct, *n (%)*	83 (50)	108 (60)	191 (55)
Incorrect, *n (%)*	82 (50)	72 (40)	154 (45)
Missing, *n*	10	6	16

* The assignment to traditional Chinese acupuncture and sham acupuncture in this table is done according to the real treatment and not as randomized. Seven patients in the sham acupuncture group were treated with traditional Chinese acupuncture.

Appendix Table 6. **All Adverse Events by Preferred Term and Treatment Group***

Preferred Term (MedDRA)	Traditional Chinese Acupuncture Group (*n* = 326), *n* (%)	Sham Acupuncture Group (*n* = 265), *n* (%)	Conservative Therapy Group (*n* = 316), *n* (%)	Total (*n* = 1007), *n* (%)
Arthralgia	16 (8.9)	15 (8.5)	13 (8.2)	44 (8.5)
Bone pain	10 (5.6)	10 (5.6)	13 (8.2)	33 (6.4)
Haematoma	12 (6.7)	18 (10.2)	1 (0.6)	31 (6.0)
Back pain	8 (4.5)	11 (6.2)	6 (3.8)	25 (4.9)
Joint lock	9 (5.0)	8 (4.5)	5 (3.1)	22 (4.3)
Condition aggravated	6 (3.4)	5 (2.8)	10 (6.3)	21 (4.1)
Localised osteoarthritis	4 (2.2)	5 (2.8)	5 (3.1)	14 (2.7)
Influenza-like illness	5 (2.8)	3 (1.7)	5 (3.1)	13 (2.5)
Sciatica	2 (1.1)	8 (4.5)	3 (1.9)	13 (2.5)
Headache	4 (2.2)	5 (2.8)	2 (1.3)	11 (2.1)
Meniscus lesion	4 (2.2)	2 (1.1)	5 (3.1)	11 (2.1)
Contusion	3 (1.7)	4 (2.3)	3 (1.9)	10 (1.9)
Joint effusion	1 (0.6)	1 (0.6)	8 (5.0)	10 (1.9)
Nasopharyngitis	6 (3.4)	3 (1.7)	1 (0.6)	10 (1.9)
Myalgia	1 (0.6)	7 (4.0)	1 (0.6)	9 (1.7)
Cervical root pain	2 (1.1)	3 (1.7)	1 (0.6)	6 (1.2)
Fall	4 (2.2)	1 (0.6)	1 (0.6)	6 (1.2)
Bronchitis acute	2 (1.1)	0 (0.0)	3 (1.9)	5 (1.0)
Gastroenteritis	2 (1.1)	2 (1.1)	1 (0.6)	5 (1.0)
Groin pain	1 (0.6)	1 (0.6)	3 (1.9)	5 (1.0)
Bursitis	1 (0.6)	3 (1.7)	0 (0.0)	4 (0.8)
Diarrhoea	0 (0.0)	2 (1.1)	2 (1.3)	4 (0.8)
Joint sprain	2 (1.1)	1 (0.6)	1 (0.6)	4 (0.8)
Neck pain	1 (0.6)	2 (1.1)	1 (0.6)	4 (0.8)
Pain in extremity	1 (0.6)	3 (1.7)	0 (0.0)	4 (0.8)
Periarthritis	2 (1.1)	1 (0.6)	1 (0.6)	4 (0.8)
Rotator cuff syndrome	2 (1.1)	0 (0.0)	2 (1.3)	4 (0.8)
Sinobronchitis	3 (1.7)	0 (0.0)	1 (0.6)	4 (0.8)
Vertigo	3 (1.7)	1 (0.6)	0 (0.0)	4 (0.8)
Vomiting	1 (0.6)	0 (0.0)	3 (1.9)	4 (0.8)
Abdominal pain upper	1 (0.6)	0 (0.0)	2 (1.3)	3 (0.6)
Epicondylitis	0 (0.0)	2 (1.1)	1 (0.6)	3 (0.6)
Gastritis	0 (0.0)	1 (0.6)	2 (1.3)	3 (0.6)
Joint swelling	2 (1.1)	1 (0.6)	0 (0.0)	3 (0.6)
Migraine	0 (0.0)	2 (1.1)	1 (0.6)	3 (0.6)
Pneumonia	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Rhinitis	0 (0.0)	3 (1.7)	0 (0.0)	3 (0.6)
Venous insufficiency	2 (1.1)	1 (0.6)	0 (0.0)	3 (0.6)
Abdominal pain lower	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Angina pectoris	1 (0.6)	1 (0.6)	0 (0.0)	2 (0.4)
Bone spur	1 (0.6)	1 (0.6)	0 (0.0)	2 (0.4)
Carpal tunnel syndrome	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Cervicobrachial syndrome	0 (0.0)	0 (0.0)	2 (1.3)	2 (0.4)
Cystitis	1 (0.6)	1 (0.6)	0 (0.0)	2 (0.4)
Depressed mood	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)
Diabetes mellitus	0 (0.0)	0 (0.0)	2 (1.3)	2 (0.4)
Dyssomnia	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.4)
Gastroduodenitis	0 (0.0)	0 (0.0)	2 (1.3)	2 (0.4)
Gout	1 (0.6)	1 (0.6)	0 (0.0)	2 (0.4)
Hypertension	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Hypoaesthesia	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Knee arthroplasty	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.4)
Metatarsalgia	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Osteoarthritis	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Osteoporosis	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.4)
Pain	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)
Pharyngitis	0 (0.0)	0 (0.0)	2 (1.3)	2 (0.4)
Phlebitis	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Post procedural haemorrhage	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)
Post procedural pain	1 (0.6)	1 (0.6)	0 (0.0)	2 (0.4)
Tendonitis	0 (0.0)	0 (0.0)	2 (1.3)	2 (0.4)
Tenosynovitis	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Acute sinusitis	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Allergy to chemicals	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Angioneurotic oedema	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)

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Appendix Table 6—**Continued**

Preferred Term (MedDRA)	Traditional Chinese Acupuncture Group (*n* = 326), *n* (%)	Sham Acupuncture Group (*n* = 265), *n* (%)	Conservative Therapy Group (*n* = 316), *n* (%)	Total (*n* = 1007), *n* (%)
Application site pain	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Arrhythmia	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Arterial bypass operation	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Arthropod bite	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Carcinoembryonic antigen increased	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Cardiac death	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac operation	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Cervix carcinoma	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Cholecystitis	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Cholelithiasis	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Chondropathy	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Coccydynia	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Cough	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Deep vein thrombosis	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Dermatitis	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Dermatitis allergic	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Dermatitis contact	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Diverticulitis	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Dyspnoea	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Dystonia	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Ear discomfort	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Exanthem	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Excoriation	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
External ear disorder	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Eye haemorrhage	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Eyelid infection	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Facet joint syndrome	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Family stress	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Fatigue	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Fibrocystic breast disease	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Fibromyalgia	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Finger crushing	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Flatulence	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Foot fracture	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Foreign body trauma	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Furuncle	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Ganglion	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Gastric haemorrhage	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Gastroenteritis bacterial	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Goitre	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Hip dysplasia	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Hyperglycaemia	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Influenza	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Injury	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Iron deficiency anaemia	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Ischaemic stroke	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Joint range of motion decreased	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Localised oedema	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Localised skin reaction	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Lung nodule	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Melaena	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Metastases to lymph nodes	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Muscle rupture	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Muscle strain	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Myocardial infarction	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Neck, shoulder, and arm syndrome	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Nodal osteoarthritis	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Oedema peripheral	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Orchitis	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Pharyngolaryngeal pain	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Piriformis syndrome	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Plantar fasciitis	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Pleural effusion	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Polyarthritis	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)

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Appendix Table 6—**Continued**

Preferred Term (MedDRA)	Traditional Chinese Acupuncture Group (*n* = 326), *n* (%)	Sham Acupuncture Group (*n* = 265), *n* (%)	Conservative Therapy Group (*n* = 316), *n* (%)	Total (*n* = 1007), *n* (%)
Prostatitis	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Pruritus	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Psychiatric symptom	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Psychosomatic disease	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Radicular pain	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Radius fracture	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Renal insufficiency	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Restless legs syndrome	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Rib fracture	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Skin fissures	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Small-cell lung cancer stage unspecified	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Spinal osteoarthritis	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Sudden hearing loss	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Synovial disorder	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Synovitis	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Temporal arteritis	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Tendon disorder	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Tenosynovitis stenosans	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Thoracic vertebral fracture	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Thrombophlebitis	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Thyroidectomy	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Toe operation	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Toothache	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Transaminases increased	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Transient ischaemic attack	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Traumatic haematoma	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Umbilical hernia	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Urinary tract infection	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Urticaria	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Varicose vein	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Viral upper respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)

* MedDRA = *Medical Dictionary for Regulatory Activities.*