

Acupuncture versus placebo versus sumatriptan for early treatment of migraine attacks: a randomized controlled trial

D. MELCHART^{1,2}, J. THORMAEHLEN¹, S. HAGER³, J. LIAO³, K. LINDE¹
& W. WEIDENHAMMER¹

From the ¹Department of Internal Medicine II, Center for Complementary Medicine Research, Technical University, Munich, Germany; ²Division of Complementary Medicine (D.M), Department of Internal Medicine, University Zurich, Switzerland; and ³Hospital for Traditional Chinese Medicine, Koetzting, Germany

Abstract. Melchart D, Thormaehlen J, Hager S, Liao J, Linde K, Weidenhammer W (Technical University, Munich, Germany; University Zurich, Switzerland; and Hospital for Traditional Chinese Medicine, Koetzting, Germany). Acupuncture versus placebo versus sumatriptan for early treatment of migraine attacks: a randomized controlled trial. *J Intern Med* 2003; **253**: 181–188.

Objectives. To investigate whether acupuncture is superior to placebo and equivalent to sumatriptan for the early treatment of an acute migraine attack.

Design. Randomized, partly double-blind (sumatriptan versus placebo) trial.

Setting. Two hospitals in Germany (one specialized in traditional Chinese medicine and one in the treatment of headache).

Subjects. A total of 179 migraineurs experiencing the first symptoms of a developing migraine attack.

Interventions. Traditional Chinese acupuncture, sumatriptan (6 mg subcutaneously) or placebo injection.

Main outcome measure. Number of patients in whom a full migraine attack (defined as severe migraine headache) within 48 h was prevented. In patients who developed a migraine attack in spite of early treatment, acupuncture and sumatriptan were

applied a second time, whilst patients initially randomized to placebo received sumatriptan.

Results. A full migraine attack was prevented in 21 of 60 (35%) patients receiving acupuncture, 21 of 58 (36%) patients receiving sumatriptan and 11 of 61 (18%) patients receiving placebo (relative risk of having a full attack 0.79 (95% CI, 0.64–0.99) for acupuncture versus placebo, and 0.78 (95% CI, 0.62–0.98) for sumatriptan versus placebo). Response to the second intervention in patients who developed a full attack was better with sumatriptan (17/31 patients who received sumatriptan twice and 37/46 patients who had had placebo first) than with acupuncture (4/31). The number of patients reporting side-effects was 14 in the acupuncture group, 23 in the sumatriptan group and 10 in the placebo group.

Conclusions. In this trial acupuncture and sumatriptan were more effective than a placebo injection in the early treatment of an acute migraine attack. When an attack could not be prevented, sumatriptan was more effective than acupuncture at relieving headache.

Keywords: acupuncture, migraine, randomized controlled trial, sumatriptan.

Introduction

Migraine is a chronic neurovascular disorder characterized by recurring attacks of severe headache and autonomic and neurological symptoms [1]. It is a major source of morbidity in Western countries [2]. Although effective drug treatments are avail-

able, a relevant proportion of patients prefer non-pharmacologic or complementary therapies for migraine. Acupuncture is amongst the most popular complementary therapies [3] and is widely used for chronic pain, including tension-type headache and migraine [4, 5]. Whilst there are a number of randomized trials investigating the effectiveness of

acupuncture for the prophylactic treatment of migraine [6], its effects on acute migraine attacks have rarely been studied.

Clinical trials of drug therapies for acute migraine typically require patients to wait until pain intensity is moderate or severe before treating with the study medication [7]. Whilst this approach facilitates research, it is likely that many patients do not in fact wait until they experience moderate or severe pain to initiate treatment, preferring instead to take medications early in the developing attack. We investigated (i) whether acupuncture is superior to a placebo injection for early treatment of migraine attacks (prevention of severe pain), and (ii) whether it is equivalent to sumatriptan. Sumatriptan, a selective 5-hydroxy-tryptamine₁ (5HT₁) agonist, has been shown to be highly effective and safe in the treatment of acute migraine attacks [8].

Methods

Study design

This study was randomized and partly double-blind (sumatriptan versus placebo-sumatriptan). Patients fulfilling all inclusion criteria were allocated randomly to one of three treatment options (see 'Interventions'). The randomization sequence was generated by a computer program ('rancode, idv', Gauting, Germany; block size 12) and concealed using sealed, opaque envelopes, which were held and distributed by the secretary (only after the patient had been included and registered by a physician) at each study centre. The information in the envelope indicated whether the patient would receive acupuncture or an injection. The medication containers were numbered consecutively. The trial was approved by the local ethics committees and was conducted in accordance with the Declaration of Helsinki.

Patients

Patients were recruited at two hospitals, one in Koetting, Bavaria, and the other in Koenigstein, Hessen. In the Koetting hospital, patients with a variety of chronic disorders are treated using traditional Chinese medicine and Western therapies in parallel by a team of Chinese and German physicians. The Koenigstein hospital specializes in the

treatment of patients whose headache disorders have not been controlled by previous outpatient care.

Recruitment took place in two stages. In the first stage, migraine patients admitted to the hospital were screened for eligibility in case they would experience an acute migraine attack. Inclusion criteria were: a diagnosis of migraine with or without aura according to the International Headache Society classification and established by a neurologist; the ability to identify premonitory symptoms of a migraine attack and to distinguish between premonitory symptoms associated with migraine and similar symptoms not associated with migraine; a history of migraine of at least 3 years; an average migraine frequency of at least two attacks per month; age between 18 and 65 years; and an electrocardiogram (ECG) without pathological signs. Exclusion criteria were: history or symptoms of ischaemic heart disease or other vascular diseases (e.g. Prinzmetal's angina, Raynaud's syndrome); diagnosis of hypertension or asthma; other neurological or psychiatric diseases; use of psychoactive drugs (e.g. hypnotics, neuroleptics, antidepressants); blood coagulation disorders; known allergy to study interventions; history of drug or alcohol abuse; and pregnancy or lactation.

In the second stage of recruitment, potentially eligible patients (according to the above criteria) were asked to contact the hospital staff immediately if they experienced premonitory or early symptoms of a migraine attack. Patients were included in the trial if they rated the intensity of their acute headache as mild or less on the validated pain scale by Heller [9, 10]. This 50-point categorial scale resembles a visual analogue scale and has the steps 0 = no pain, 1–10 = very mild pain, 11–20 = mild pain, 21–30 = moderate pain, 31–40 = severe pain, and 41–50 = very severe pain. Patient who had been treated with sumatriptan or ergotamine in the last 24 h were excluded. All patients provided written informed consent.

Interventions

Acupuncture was performed by experienced Chinese acupuncturists trained at the Beijing University for Traditional Chinese Medicine. The acupuncture points used were mainly Gallbladder (GB) 41, GB 20, GB 15, GB 14, GB 10, GB 8, Large Intestine

(LI) 4, Liver 3, Sanjiao 5, Du-Mai 20 and Extra 2 Taiyang, along with points for individual migraine-associated symptoms. Point selection was usually bilateral, and needles were given manual manipulation to achieve a numb, warm feeling around the acupuncture point (de qi). Needles in two sizes (0.3×40 and 0.25×25 mm) were used. The median duration of the acupuncture treatment was 1.5 h (range, 0.5–2.1). Sumatriptan (6 mg in 1 mL NaCl solution) or placebo (1 mL NaCl solution), identically packaged, was injected subcutaneously. All treatments were applied immediately after randomization. If a full migraine attack (definition see study procedures and endpoints) developed in spite of treatment, then the intervention was repeated for patients in the acupuncture and sumatriptan groups; patients in the placebo group received sumatriptan. If this second treatment was unsuccessful (<50% pain reduction 2 h after treatment), then patients received 500–1000 mg acetylsalicylic acid i.v. or 500 mg metamizole i.v. as an escape medication.

Study procedures and endpoints

At screening, a general medical history and a detailed headache history were taken. Patients underwent a physical examination and 12-lead ECG. After inclusion in the trial, patients were asked to assess headache intensity, accompanying symptoms and side-effects 1, 2, 6, 12, 18, 24, 36 and 48 h after start of the treatment. The main outcome measure was the number of patients in whom a full migraine attack within 48 h was prevented. An attack was defined as fully developed if the patient rated headache as severe (more than 30 on the 50-point scale by Heller = severe migraine headache). Response to the second intervention was defined as at least 50% pain reduction 2 h after treatment.

Statistical analysis

The relative frequency of patients developing a full migraine attack was statistically analysed using a hierarchical approach in the sense of a closing test procedure [11]. The analysis was conducted on an intention-to-treat basis. As a first step, the null hypothesis that placebo is superior or equal to acupuncture had to be tested (one-tailed Fisher's exact test). As a preplanned interim analysis had

been performed after recruitment of 75 patients, the nominal alpha-level was adjusted according to O'Brien-Fleming to $\alpha = 4.8\%$. If and only if this hypothesis could be rejected, i.e. if acupuncture were superior to placebo, then the equivalence of acupuncture and sumatriptan was to be tested as a second step. Given a range of equivalence of 15%, the hypothesis that acupuncture is 'not more than negligibly inferior' to sumatriptan was tested by a one-tailed Fisher's test for equivalence [12].

Time to fully developed migraine attack was analysed using a survival model (Kaplan–Meier estimation). The differences between 'survival' functions were tested by the log rank test.

For hypothesis testing, SAS was used as statistical software.

Results

Between December 1996 and March 1999, a total of 477 patients were screened, of whom 179 were enrolled in the study (see Fig. 1). Sixty patients were allocated to acupuncture, 58 to sumatriptan and 61 to placebo. All patients could be analysed for the main outcome measure. Patient and baseline characteristics were similar in the three groups (see Table 1). Most patients had mild headache (11–20 points on the Heller scale) at inclusion in the study.

A full migraine attack within 48 h was prevented in 21 of 60 (35%) patients receiving acupuncture, 21 of 58 (36%) patients receiving sumatriptan and 11 of 61 (18%) patients receiving the placebo injection. The difference between acupuncture and placebo was statistically significant (Fisher's exact test, $P = 0.028$). The relative risk of having a full attack was 0.79 (95% CI, 0.64–0.99) for acupuncture versus placebo and 0.78 (95% CI, 0.62–0.98) for sumatriptan versus placebo.

The response rates in both the sumatriptan and the acupuncture group were lower than expected in the planning of the study. Based on the 15% equivalence range defined in the protocol, the hypothesis that acupuncture is not equivalent to sumatriptan was refused ($P = 0.019$). The relative risk of having a full attack (acupuncture versus sumatriptan) was 1.03 (95% CI, 0.64–1.68).

Figure 2 shows the incidence of attacks in relation to time (time-to-event analysis, log rank test). In this analysis both sumatriptan ($P < 0.001$) and acupuncture ($P = 0.02$) were superior to placebo

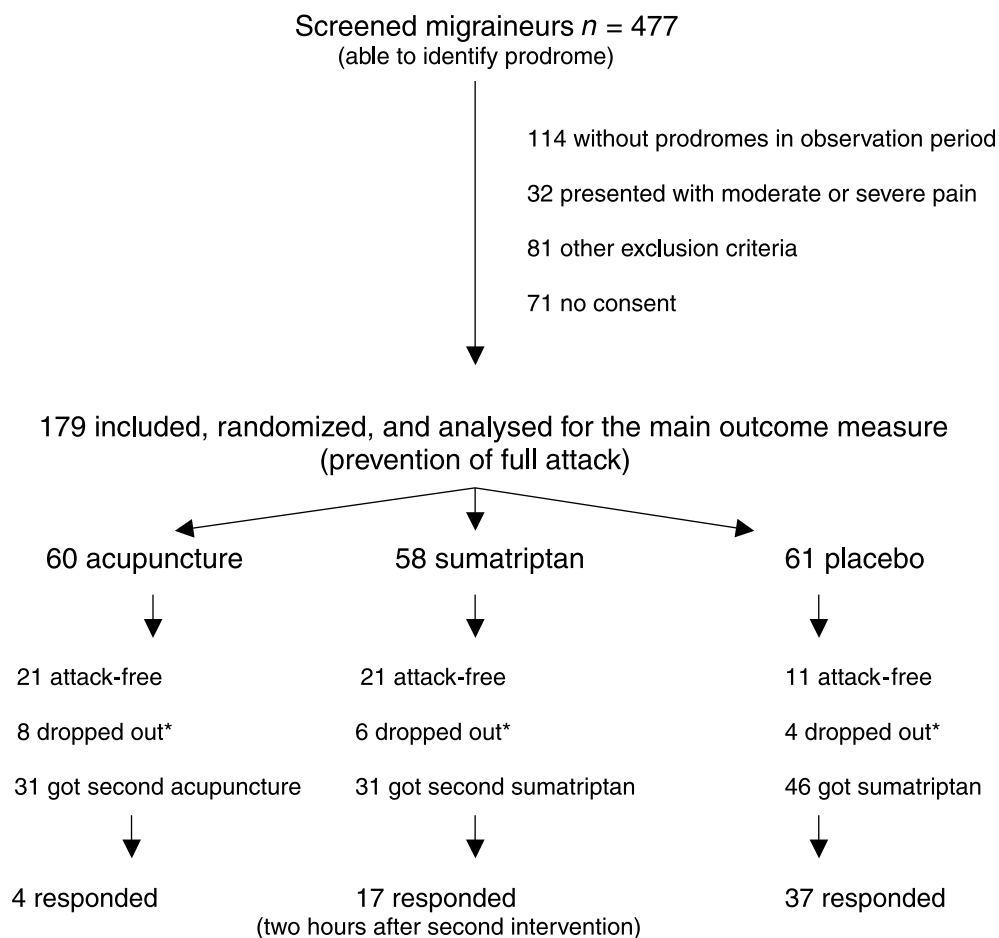


Fig. 1 Trial profile, *refused the second study intervention.

Table 1 Patient and baseline characteristics

	Acupuncture $n = 60$	Sumatriptan $n = 58$	Placebo $n = 61$
Age (years; mean $\pm$ SD)	43.5 $\pm$ 9.4	45.4 $\pm$ 9.6	44.4 $\pm$ 9.8
Female sex	53 (88%)	52 (90%)	49 (80%)
Duration of migraine (years; mean $\pm$ SD)	21.4 $\pm$ 11.9	22.2 $\pm$ 9.6	20.9 $\pm$ 9.6
Attacks per month (mean $\pm$ SD)	7.0 $\pm$ 6.3	6.4 $\pm$ 5.4	5.3 $\pm$ 3.1
Migraine without aura	52 (87%)	49 (84%)	54 (89%)
Previous acupuncture treatment*	47 (78%)	46 (79%)	46 (75%)
With good success	10	18	14
With moderate success	9	8	10
With little or no success	24	20	21
Cannot tell	4	—	1
Previous use of sumatriptan	23 (38%)	25 (43%)	30 (49%)
Headache intensity at inclusion [median (range)]	17 (4–10)	18 (3–20)	18 (0–20)
Patients with no pain (0 on the Heller scale)	—	—	1 (2%)
Patients with very mild pain (1–10)	6 (10%)	9 (16%)	4 (7%)
Patients with mild pain (11–20)	54 (90%)	49 (84%)	56 (92%)

*No patient had acupuncture in the month prior to the study.

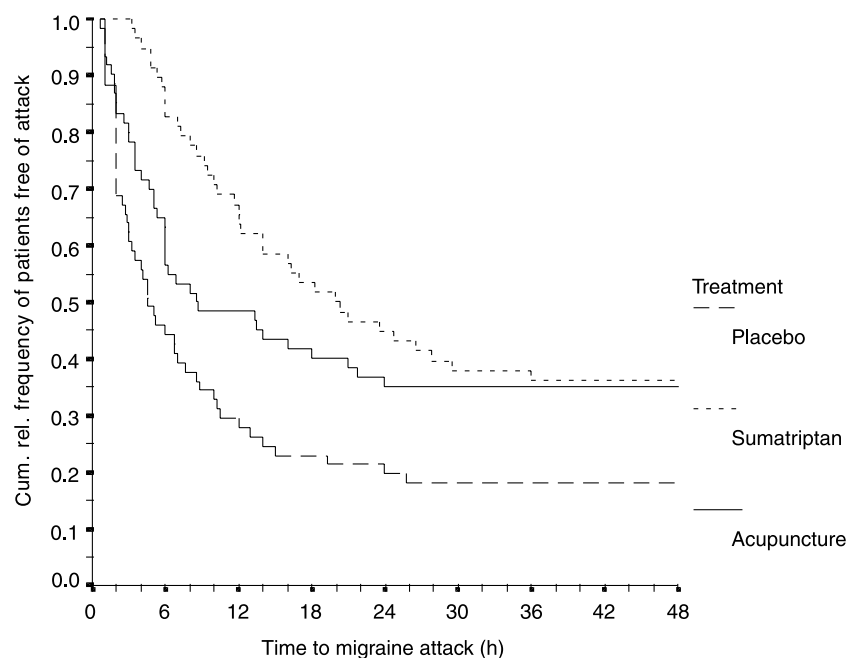


Fig. 2 Proportion of patients free of attack (severe pain) during the observation period of 48 h.

Table 2 Adverse events

	Acupuncture	Sumatriptan	Placebo
Number of patients with adverse events	14	23	10
Elevated blood pressure (syst. and/or diast.)	13	22	8
Chest pain (pressure, tightness)	—	4	—
Heat sensation	—	2	—
Dizziness, vertigo	—	2	1
Others	3	6	1
Total number of adverse events reported	16	36	10

injection. Whilst there was no statistically significant difference between the two active interventions, the curves suggest that patients receiving sumatriptan remained attack-free longer ($P = 0.218$). The median time to attack was 19.9 h (95% CI, 10.9–28.8) with sumatriptan, 8.5 h (95% CI, 0–17.8) with acupuncture and 4.6 h (95% CI, 2.4–6.8) with placebo injection. There were no significant differences between the groups regarding migraine-associated symptoms.

The number of patients who were painfree (0 points on the Heller scale) 1 h after start of the intervention was 1 (2%) in the acupuncture group, 6 (10%) in the sumatriptan group and 0 in the placebo injection group (P -values acupuncture versus sumatriptan 0.059, acupuncture versus placebo 0.496, sumatriptan versus placebo 0.012, Fisher's exact test). The respective numbers at 2 h were 4 (7%), 14 (24%) and 0 (P -values acupuncture versus

sumatriptan 0.010, acupuncture versus placebo 0.057, sumatriptan versus placebo <0.001), and at 6 h 10 (17%), 20 (35%) and 3 (5%) (P -values acupuncture versus sumatriptan 0.034, acupuncture versus placebo 0.044, sumatriptan versus placebo <0.001).

A total of 108 patients who experienced a full attack received a second study intervention according to the protocol. Pain reduction of 50% or more was reported 2 h later by 4 of 31 (13%) patients receiving a second acupuncture treatment, 17 of 31 (55%) patients receiving a second sumatriptan injection, and 37 of 49 (80%) patients who received sumatriptan after having initially received a placebo injection.

Adverse events were reported for 13 patients in the acupuncture group, 23 in the sumatriptan group and 10 in the placebo injection group (see Table 2). All but two adverse events were classified

as minor and transient and without need for intervention. In the sumatriptan group, one patient received an antihypertensive treatment with 10 mg sublingual nifedipine. In the acupuncture group, one needle insertion was too painful, and the needle had to be removed. The most frequently observed adverse event in all three treatment groups was elevated blood pressure (>150/90 mm Hg). Chest-related symptoms such as chest pain, tightness and heaviness, as well as heat sensation after the injection, occurred only in the sumatriptan group.

Discussion

To the best of our knowledge this is the first randomized controlled trial comparing acupuncture with a standard drug and a placebo injection for the early treatment of an acute migraine attack. We found that both acupuncture and sumatriptan were more effective than a placebo injection to prevent the development of a full attack. More patients were painfree 2 h after start of the treatment with sumatriptan than with acupuncture or placebo injection, and sumatriptan was superior to acupuncture at relieving headache once a migraine attack had fully developed.

When interpreting our results a number of limitations have to be kept in mind. First, the patients participating in the trial were a highly selected sample. They sought inpatient care at the study centres because their headache complaints had not been controlled sufficiently by outpatient care in the past. In Germany, there are several (conventional and unconventional) centres providing inpatient care for such patients. A large proportion of the study participants had already tried acupuncture in the past. Interestingly, only a minority of these reported positive experiences. As the participants in our study cannot be considered representative for the average migraine sufferers the generalizability of our findings is unclear.

Second, the study did not include a sham acupuncture control group. Such a forth group was considered in the planning phase, but not included after discussion with the peer review group of the funding body for the following reasons: (i) the recruitment target of 180 patients was considered as the upper possible limit; (ii) sham acupuncture interventions are difficult to define as various components (place, depth, stimulation) might

contribute to the specificity of the effect; (iii) there is some evidence that sham acupuncture interventions are not physiologically inert [13]; (iv) blinding of the therapist is hardly possible; (v) in our patient sample the majority of patients had acupuncture in the past. Most sham acupuncture modalities (for example, superficial needling without achieving the characteristic de-qi sensation) are likely to be distinguished from true acupuncture by experienced patients. Telescope needles which are inserted into a plaster and do not penetrate the skin [14] were not yet available when the study was planned but would have been impractical anyhow as a number of acupuncture points for migraine are located in hairy areas. The lack of a sham acupuncture control group in our study implies that we cannot say whether the strategy tested was superior to a sham acupuncture strategy. Furthermore, patients receiving acupuncture were not blinded, so we cannot rule out completely that they experienced or assessed their pain intensity differently from patients in the other two groups.

Third, only nonresponders received a second intervention. As these nonresponders were not randomized a second time and all patients knew on which treatment they were, the results of this part of the study must be considered exploratory. However, we think that these results are so clear-cut that they can be interpreted in a clinically meaningful way.

In most clinical trials on acute migraine the intervention has been applied only when pain has become moderate or severe. In this situation response rates around 80% have been reported for subcutaneous sumatriptan [15–17]. However, some of the patients included in such trials violated the protocol and started treatment when headache was still mild. These patients were excluded from the original analyses, but in 2000 Cady *et al.* published re-analyses of the respective data sets from four trials [18, 19]. The proportion of patients who were pain-free 2 h after taking sumatriptan 50- or 100-mg tablets was between 50% and 73%. The lower proportion of responders in our trial might be explained by the fact that our inpatient sample probably represents a group of patients who are difficult to treat. As there is no comparable data available we cannot say whether this applies also to acupuncture. However, it might be that the proportion of responders to early treatment would be

higher in a 'normal' population of migraine sufferers both for sumatriptan and for acupuncture.

Adverse events were more frequent in the sumatriptan group than in the other two groups. In the literature, rates of adverse events after treatment with sumatriptan s.c. vary from 27% [20] to 85% of patients [21]. In our trial, elevated blood pressure was the most commonly reported adverse event in all three groups, but it occurred most frequently in the sumatriptan group. Previously published trials reported similar findings for sumatriptan in healthy subjects or migraineurs without hypertension [22] and in hypertensive patients who were being treated with antihypertensive medications [23]. Four patients in the sumatriptan group experienced chest-related symptoms. The incidence and type of these symptoms were consistent with other clinical trials [24, 25].

In conclusion, our trial provides evidence that both s.c. sumatriptan and acupuncture are more effective than a placebo injection in the early treatment of acute attacks in a population of hospitalized migraine sufferers. However, given the modest effect of acupuncture on the reduction of pain intensity, its limited availability and the necessity to seek a provider at short notice, it does not seem to be a realistic routine option for acute migraine management in an outpatient setting. Treatment with triptans and other analgetics has been shown to be effective and is much easier to apply. Future research on acupuncture for migraine should focus on prophylactic treatment and self-management strategies with acupressure for acute attacks.

Acknowledgements

Both sumatriptan and the placebo were kindly provided by GlaxoWellcome, Bad Oldesloe, Germany. We wish to thank Drs Y. Liu, L.X. Tang, G.F. Xing and G.R. Zhang as well as the German physicians at the T.C.M. hospital Koetzting and Dr Brand at the migraine hospital, Koenigstein, for their support. T. Draczynski and F. Worku contributed in the planning of the study. R. Gray helped to get our German English acceptable for native English speakers. The statistical analysis of the main outcome measure was performed by the Biometrisches Zentrum für Therapiestudien, Munich. The study was supported by a grant from the B.M.B.F., the

German ministry of education and research (01 KT 9408/7). The study is part of the M.D. thesis of Johannes Thormaehlen.

References

- 1 Ferrari MD. Migraine. *Lancet* 1998; **351**: 1043–51.
- 2 Rasmussen BK. Epidemiology and socio-economic impact of headache. *Cephalgia* 1999; **19**(Suppl. 25): 20–3.
- 3 White AR, Resch KL, Ernst E. Complementary medicine: use and attitudes among GPs. *Fam Pract* 1997; **14**: 302–6.
- 4 Wadlow G, Peringer E. Retrospective survey of patients of practitioners of traditional Chinese acupuncture in the UK. *Complement Ther Med* 1996; **4**: 1–7.
- 5 Hayhoe S, Box H. A questionnaire on medical acupuncture practice. *Acup Med* 1997; **15**: 96–9.
- 6 Melchart D, Linde K, Fischer P *et al.* Acupuncture for recurrent headaches: a systematic review of randomized controlled trials. *Cephalgia* 1999; **19**: 779–86.
- 7 Tfelt-Hansen P. How to define the best efficacy parameters for migraine. *Cephalgia* 1997; **17**(Suppl. 17): 6–8.
- 8 Tfelt-Hansen P. Efficacy and adverse events of subcutaneous, oral, and intranasal sumatriptan used for migraine treatment: a systematic review based on number needed to treat. *Cephalgia* 1998; **18**: 532–8.
- 9 Goebel H. Schmerzmessung. Theorie-Methodik-Anwendung bei Kopfschmerz. Stuttgart: Gustav Fischer Verlag, 1992; 76–9.
- 10 Heller O. Theorie und Praxis des Verfahrens der Kategorienunterteilung (KU). In: Heller O ed. *Forschungsbericht 1981*. Würzburger Psychologisches Institut Würzburg, 1982.
- 11 Marcus R. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* 1976; **63**: 655–60.
- 12 Welke S. Statistische Methoden zum Nachweis von Äquivalenz. Stuttgart: Gustav Fischer Verlag, 1994.
- 13 Vincent C, Lewith G. Placebo controls for acupuncture studies. *J Roy Soc Med* 1995; **88**: 199–202.
- 14 Streitberger K, Kleinhenn J. Introducing a placebo needle into acupuncture research. *Lancet* 1998; **352**: 364–5.
- 15 Schoenen J, Bulcke J, Caekebeke J *et al.* Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device: comparison with customary treatment in an open, longitudinal study. *Cephalgia* 1994; **14**: 55–63.
- 16 Winner P, Ricalde O, Le Force B, Saper J, Margul B. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol* 1996; **53**: 180–4.
- 17 Göbel H, Heinze A, Stolze H, Heinze-Kuhn K, Lindner V. Open-labeled long-term study of the efficacy, safety, and tolerability of subcutaneous sumatriptan in acute migraine treatment. *Cephalgia* 1999; **19**: 676–83.
- 18 Cady RK, Lipton RB, Hall C, Stewart WF, O'Quinn S, Gutterman D. Treatment of mild headache in disabled migraine sufferers: results of the Spectrum study. *Headache* 2000; **40**: 792–7.
- 19 Cady RK, Sheftell F, Lipton RB *et al.* Effect of early intervention with sumatriptan on migraine pain: retrospective analyses of data from three clinical trials. *Clin Ther* 2000; **22**: 1035–48.
- 20 Henry P, d'Allens H. Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. *Headache* 1993; **33**: 432–5.

- 21 Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA* 1991; **265**: 2831–5.
- 22 MacIntyre PD, Bhargava B, Hogg KJ, Gemmill JD, Hillis WS. Effect of subcutaneous sumatriptan, a selective 5HT₁ agonist, on the systemic, pulmonary, and coronary circulation. *Circulation* 1993; **87**: 401–5.
- 23 Jhee SS, Salazar DE, Ford NF, Fulmor IE, Sramek JJ, Cutler NR. A double-blind, randomized, crossover assessment of blood pressure following administration of avitriptan, sumatriptan, or placebo to patients with mild or moderate hypertension. *Cephalalgia* 1999; **19**: 95–9.
- 24 Akpunonu BE, Mutgi AB, Federman DJ *et al.* Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: a multicenter study. *Ann Emerg Med* 1995; **25**: 464–9.
- 25 Diener HC. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double blind, double-dummy, randomized, multicenter, parallel-group study. *Cephalalgia* 1999; **19**: 581–8.

Received 29 July 2002; revision received 4 October 2002; accepted 30 October 2002.

Correspondence: Dr Dieter Melchart, Department of Internal Medicine II, Center for Complementary Medicine Research, Technical University, Kaiserstr. 9, 80801 Munich, Germany (fax: +49 89 393484; e-mail: dieter.melchart@lrz.tu-muenchen.de).