

# A Randomized Clinical Trial on Acupuncture Versus Best Medical Therapy in Episodic Migraine Prophylaxis: The Acumigran Study

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## Research article

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# Abstract

## Background

A large corpus of evidence has reported encouraging results for acupuncture as a prophylaxis therapy of migraine. However, trials investigated the efficacy of acupuncture in comparison to pharmacological treatment in episodic migraine showed conflicting results. The aim of the study was to evaluate if acupuncture is as effective as evidence based pharmacological drugs in episodic migraine prophylaxis.

## Methods

This is a randomized controlled clinical study. Patient suffering from migraine without preventive treatment in the past three months were recruited. After the run-in period, episodic migraineurs were assigned randomly to two groups: the acupuncture group (A) was treated with 12 sessions of acupuncture and the pharmacological group (B) was treated with the most appropriate medication for each patient. Headache frequency was compared at baseline and at the end of treatment. Both groups were evaluated 3- and 6-months after treatment.

## Results

A total of 148 patients (24 males and 124 females) were enrolled in the study. Out of these, 69 were randomized to A and 66 to B. At baseline no significant differences were found between the two groups. The 15.5% of patients (21/135) interrupted the treatment, especially those randomized to B. After 4 months, the migraine frequency decreased from  $8.58 \pm 3.21$  to  $6.43 \pm 3.45$  in A and from  $8.29 \pm 2.72$  to  $6.27 \pm 4.01$  in B. Headache frequency decreased significantly after treatment without differences between the two groups (time-effect:  $p < 0.001$ ; group effect:  $p = 0.332$ ; interaction time-group effects:  $p = 0.556$ ). About 34% of patients showed a reduction of headache days by at least 50% after the treatment. The improvements observed at the end of treatment persisted in 57.3% (59/103) after 3 months and in 38.8% (40/103) after 6 months, especially in patients randomized to A.

## Conclusions

Our trial is the first one comparing acupuncture with the more appropriate pharmacological treatment for migraine prophylaxis. Data suggested that acupuncture could be adopted as a migraine prophylaxis and seem to be slightly superior to pharmacological treatment in compliance and rate of adverse events.

## Background

Migraine is a common disabling primary headache disorder [1], affecting approximately 15% of adults in Western countries. Its prevalence increases at the age of 35–39 years and in female sex. It affects adults in an active phase of their life, leading to a significant disability and loss of quality of life, with relevant social and economic costs [2–3].

The treatment of migraine includes acute therapies, that aim to reduce the intensity of pain of each migraineous attack, and preventive therapies that should decrease the frequency of headache appearance [4–6].

Despite the great progress in pharmacologic treatment, patients often remain unsatisfied because of the low pain control or the associated unacceptable side-effects [7].

In the past decades, acupuncture has been pointed out a valuable non-pharmacological tool in patients with migraine and its use in clinical practice has been increasing in Western countries. A large corpus of evidence has reported encouraging results for acupuncture as a prophylaxis therapy of migraine [8–10]. However, trails investigated the efficacy of acupuncture in comparison to pharmacological treatment in episodic migraine showed conflicting results, mainly due to differences in population characteristics, study design and outcome measures [10–16]. Moreover, the majority of these studies compared acupuncture with monotherapy as prophylactic treatment and findings comparing acupuncture with the best medical treatment are lacking.

## Methods

### Aim, design and setting of the study

The aim of the study was to evaluate if acupuncture is as effective as evidence based pharmacological drugs in migraine prophylaxis. This is a randomized, controlled, open-label, multicenter study. Two Italian Tertiary Headache Centres participated in the study (the Headache Centre of IRCCS Istituto delle Scienze Neurologiche di Bologna and the Headache Centre of the University of Parma).

### Participants

Patients referred to the Headache Centres from 2012 to 2016 were consecutively recruited.

Inclusion criteria for the eligibility in the study were the following: 1) age  $\geq$  18 years old; 2) ability to give verbal and written informed consent; 3) episodic Migraine with and without aura as defined by the International Headache Society [1]; 4) absence of preventive treatment in the preceding three months.

Exclusion criteria included: 1) severe psychiatric disease; 2) alcohol or drugs addiction; 3) serious ongoing physical illness; 4) inability to sign the informed consent; 5) pregnancy and breast-feeding,

Patients with contraindication to use acupuncture or prophylactic therapies for comorbidities were also excluded.

### Protocol and visit assessments

Figure 1 illustrates the study design. Visits occurred at baseline (preliminary visit T0), 1 month after baseline (T1), 4 months after treatment program (T2), then at 3 months (T3) and 6 months (T4) after the end of treatment (Fig. 1).

Patients with episodic migraine with and without aura without preventive treatment in the preceding three months were evaluated in an outpatient visit at baseline (T0). After one-month run-in period, eligible patients were randomized (T1) to acupuncture group (A) or pharmacological group (B) 1:1.

Patients in group A received 12 sessions of acupuncture. The first session included a standardized investigation from acupuncturist including a traditional Chinese medicine diagnosis for syndromes. Acupuncture was carried out twice in the first week and weekly for the next 10 sessions and consisted of semi-standardized treatments including some basic obligatory points (LR 3 *taichong*, GB 34 *yanglingchuan*, SP 6 *sanyinjiao*, LI 4 *hegu*, TE 5 *weiguan*, GV 20 *baihui*) and additional

individualized points chosen by the physicians on the basis of diagnosis and pain localization (ST 8 *touwei*, BL 2 *zanzhu*, GB 4 *hanyan*, GB 8 *shuaigu*, GB 20 *fengchi*, BL 12 *fengmen*). Acupuncturists were highly qualified medical doctor members of A.M.A.B. (ASSOCIAZIONE MEDICI AGOPUNTORI BOLOGNESI-Scuola Italo Cinese di Agopuntura) receiving the same training on Acupuncture and Chinese Medicine.

Patients in group B was treated with the most appropriate prophylactic medication for 4 months. Prophylactic treatment was chosen based on the efficacy and side effects of previous treatments, comorbidity and patients' preferences, as in the best clinical practice [4–6]. One telephone interview was performed by trained nurse after 2 months of therapy in order to investigate compliance and adverse events. All patients were allowed to treat acute headaches as needed. After baseline, concomitant treatment for comorbidities should not be changed.

Subjects were assigned sequentially to group A or B when admitted to the outpatients visit T1 receiving a computer-generated random medication code number. The random allocation sequence was not generated by researchers who assigned participants to interventions.

At T2 prophylactic treatment (both A or B) were stopped. Both groups were evaluated 3- and 6-months after treatment (T3-T4).

A clinical diary in which patients recorded all headache attacks and days, and rescue medication intake for migraine during the study period, was given at T0 and checked at every follow-up visit. At the time of enrolment patients filled in a questionnaire on preference for acupuncture or pharmacological treatment. Depressive and anxious symptoms [17–18], degree of disability (Migraine Disability Assessment Score, MIDAS) [19] and quality of life (36-Item Short-Form Health Survey, SF-36) [20] were evaluated during every visits. At the end of treatment a satisfaction questionnaire was collected. All patients were interviewed and examined by neurologists expert in headaches.

## Outcome measures

Primary outcome measure was the difference in number of days with migraine between T1 and T2 as reported by the patient in the headache diary.

Predefined secondary outcomes included: proportion of treatment responders (migraineurs with a reduction of headache days by at least 50% documented in a headache diary), number of migraine attacks, number of rescue medication, number of patients which discontinued the trial, migraine frequency (days and attacks) and rescue medication during follow-up.

## Statistics

Normality of continuous parameters distribution was checked using the Skewness-Kurtosis test, variables were expressed as mean  $\pm$  standard deviation or median along with interquartile ranges when appropriate. Continuous variables were compared by using t-test or Wilcoxon rank-sum, as appropriate. Categorical variables were described by their absolute and/or relative frequencies and compared using Chi square test.

Repeated measures ANOVA was performed to investigate significant main effects for all patients across time (T1, T2, T3, T4). A p-value lower than 0.05 (2-sided) was considered significant. Statistical analyses were performed using the statistical software STATA®, version 14.0.

## Results

The study flow-chart is shown in Fig. 2. A total of 187 consecutive patients (37 males and 150 females) were eligible for the study. Of these, 148 patients (24 males and 124 females) were enrolled in the study and 135 (21 males and 114 females) were randomized: 103 patients completed the treatment (18 males and 85 females), 23 patients discontinued the treatment (3 males and 20 females) and 9 females were lost to follow-up.

Finally, 59 patients (10 males and 49 females) and 40 patients (6 males and 34 females) have undergone the T3 and T4 visits, respectively.

A total of 39 (20.9%, 13 males and 26 females) patients declined to participate at the study: 31 declined because they should not undergo to Acupuncture (20 worker patients refused for time reasons, 5 suffered by fear of needling, 3 could not participate to acupuncture section for distance reason, 1 have just been previously treated with acupuncture for migraine, 2 should accept only conventional treatment), 3 declined because they should not intake pharmacological treatment, 1 declined to participate to a clinical study, 4 declined for unknown reasons.

Out of 142 patients enrolled in the study, 13 were not randomized (9 did not meet inclusion criteria, 3 moved to another town and 1 was pregnant).

Out of 135 randomized patients, 32 dropped out: 7 withdrew their consent for study participation directly after randomization to B group (refused the prophylaxis drugs), 2 showed adverse event to drugs, 4 did not tolerate acupuncture, 8 (2 patients randomized to A and 6 randomized to B) showed a poor compliance, 3 (1 patients randomized to A and 2 randomized to B) interrupted treatment for pregnancy and 8 (5 patients randomized to A and 3 randomized to B) patients were lost to the follow-up. The

adverse events reported with pharmacological drugs were mild and reversible but two required the suspension of the treatment: one patients developed depression after introduction of flunarizine and another one discovered mild hypertransaminasemia (already presented in the past) and stopped topiramate to further investigate its medical condition.

Out of 135 randomized patients (21 males and 114 females, mean age mean  $\pm$  SD:  $34.2 \pm 16.8$  years), 69 were randomized to A and 66 to B.

Among patients randomized to B group, 17 (25.8%) received amitriptyline, 7 (10.6%) beta-blockers (4.5% atenolol and 6.1% propranolol), 15 (22.7%) flunarizine, 9 (13.6%) topiramate, 3 (4.5%) pizotiphen, 2 (3.0%) valproic acid, 1 (1.5%) duloxetine, 11 (16.7%) Riboflavine (Vitamine B2) and 2 (3.0%) a combination of others nutraceutical drugs according to international guideline [5–6]. Demographic and clinical characteristics of the two groups are shown in Table 1. There were not differences in term of sociodemographic variables, age at migraine onset, diagnosis, headache frequency (days and attacks per month), frequency of rescue medications intake (number per month), previous pharmacological and non-pharmacological treatment, scores at Zung scales, MIDAS and SF-36. Medical conditions did not differ between the two groups. There were not differences in patients preference questionnaire for acupuncture or pharmacological treatment between the two groups at the time of enrollment.

Table 1  
Demographic and baseline clinical characteristics of the study sample

		TOTAL	TREATMENT GROUPS		p value
			A: ACUPUNCTURE	B:PHARMACOLOGICAL	
<b>Sample</b>	<i>N (%)</i>	135	69 (51.1)	66 (48.9)	
<b>Age (years)</b>	<i>mean ± SD</i>	34.2 ± 16.8	33.6 ± 17.4	34.7 ± 16.5	0.698
<b>Sex</b>					0.899
<b>Males</b>	<i>N (%)</i>	21 (15.6)	11 (15.9)	10 (15.2)	
<b>Females</b>	<i>N (%)</i>	114 (84.4)	58 (84.1)	56 (84.8)	
<b>Marital Status</b>					0.499
<b>Single</b>	<i>N (%)</i>	35 (25.9)	15 (21.7)	20 (30.3)	
<b>Married</b>	<i>N (%)</i>	88 (65.2)	47 (68.1)	41 (62.1)	
<b>Separated/Divorced</b>	<i>N (%)</i>	12 (8.9)	7 (10.2)	5 (7.6)	
<b>Widower</b>	<i>N (%)</i>	0 (0.0)	0 (0.0)	0 (0.0)	
<b>Years of Education</b>	<i>mean ± SD</i>	13.6 ± 3.4	13.1 ± 3.4	14.0 ± 3.3	0.127
<b>Employment</b>					0.479
<b>Employee</b>	<i>N (%)</i>	108 (80.0)	57 (82.6)	51 (77.2)	
<b>Unemployed</b>	<i>N (%)</i>	6 (4.4)	1 (1.5)	5 (7.6)	
<b>Housewife</b>	<i>N (%)</i>	9 (6.7)	5 (7.2)	4 (6.1)	
<b>Student</b>	<i>N (%)</i>	9 (6.7)	4 (5.8)	5 (7.6)	
<b>Retired</b>	<i>N (%)</i>	3 (2.2)	2 (2.9)	1 (1.5)	
<b>Smoke status</b>					0.710
<b>Non-smoker</b>	<i>N (%)</i>	92 (68.2)	49 (71.1)	43 (65.2)	
<b>Smoker</b>	<i>N (%)</i>	18 (13.3)	9 (13.0)	9 (13.6)	
<b>Ex-smoker</b>	<i>N (%)</i>	25 (18.5)	11 (15.9)	14 (21.2)	

**Legend:** IQR: interquartile range; med: median; MOH: medication overuse headache; N: sample size; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; SD: standard deviation

		TOTAL	TREATMENT GROUPS		
<b>Alcohol status</b>					
No-alcohol intake	<i>N (%)</i>	44 (32.6)	25 (36.2)	19 (28.8)	0.647
Occasionally	<i>N (%)</i>	75 (55.6)	36 (52.2)	39 (59.1)	
Frequent	<i>N (%)</i>	16 (11.8)	8 (11.6)	8 (12.1)	
Age at Migraine Onset (years)	<i>mean ± SD</i>	16.2 ± 8.6	16.9 ± 8.2	15.4 ± 8.9	0.2867
<b>Diagnosis</b>					
Migraine without aura	<i>N (%)</i>	114 (84.4)	55 (79.7)	59 (89.3)	0.063
Migraine with and without aura	<i>N (%)</i>	12 (8.9)	10 (14.5)	2 (3.0)	
Migraine without aura + Tension type headache	<i>N (%)</i>	9 (6.7)	4 (5.8)	5 (7.6)	
<b>Previous prophylactic treatment</b>					
Yes	<i>N (%)</i>	72 (53.3)	38 (55.1)	34 (51.5)	0.679
No	<i>N (%)</i>	63 (46.7)	31 (44.9)	32 (48.5)	
<b>Efficacy of previous pharmacological treatment</b>					
Yes	<i>N (%)</i>	23 (17.0)	11 (15.9)	12 (18.2)	0.483
No	<i>N (%)</i>	44 (35.6)	25 (36.2)	19 (28.8)	
<b>Efficacy of previous non-pharmacological treatment</b>					
Yes	<i>N (%)</i>	11 (8.1)	5 (7.25)	6 (9.1)	0.330
No	<i>N (%)</i>	5 (3.7)	1 (1.45)	4 (4.1)	
Headache frequency (attacks/month)	<i>mean ± SD</i>	5.8 ± 2.2	5.7 ± 2.3	5.8 ± 2.1	0.8079
Headache frequency (days/month)	<i>mean ± SD</i>	8.4 ± 2.9	8.6 ± 3.2	8.3 ± 2.7	0.5700

**Legend:** IQR: interquartile range; med: median; MOH: medication overuse headache; N: sample size; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; SD: standard deviation

		TOTAL	TREATMENT GROUPS		
Frequency of medication intake (number/month)	<i>mean ± SD</i>	8.2 ± 4.5	8.2 ± 4.7	8.3 ± 4.3	0.9263
Migraine disability assessment score	<i>Med (IQR)</i>	21; 10–44	20; 14–42	22; 8.5–44.5	0.8317
Zung Self-Rating Depression Scale	<i>mean ± SD</i>	37.3 ± 8.2	37.2 ± 8.6	37.5 ± 7.8	0.8332
Zung Self-Rating Anxiety Scale	<i>mean ± SD</i>	37.2 ± 5.4	37.7 ± 5.4	36.6 ± 5.4	0.2872
<b>SF-36 Scale</b>					
Social Role	<i>Med (IQR)</i>	62.5 (50–75)	62.5 (50–75)	62.5 (50–75)	0.7927
Physical Functioning	<i>Med (IQR)</i>	90 (80–100)	90 (80–95)	90 (80–100)	0.6468
Bodily Pain	<i>Med (IQR)</i>	41 (32–51)	41 (32–51)	41 (32–52)	0.5455
Emotional Role	<i>Med (IQR)</i>	66.67 (33.33–100)	66.67 (33.33–100)	66.67 (33.33–100)	0.5705
Physical Role Functioning	<i>Med (IQR)</i>	37.5 (0–75)	25 (0–75)	50 (0–75)	0.4704
General health perception	<i>Med (IQR)</i>	62 (45–77)	62 (45–77)	62 (46–74.5)	0.7193
Mental health	<i>Med (IQR)</i>	64 (52–76)	64 (52–76)	64 (56–72)	0.9080
Vitality	<i>Med (IQR)</i>	55 (40–65)	55 (45–65)	55 (40–62.5)	0.7947
<b>Legend:</b> IQR: interquartile range; med: median; MOH: medication overuse headache; N: sample size; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; SD: standard deviation					

The number of headache days decreased significantly after treatment without differences between groups (headache frequency, time-effect:  $p < 0.0001$ ,  $F = 22.61$  ; group effect:  $p = 0.6099$ ,  $F = 0.26$ ; interaction days-group effects:  $p = 0.8768$ ,  $F = 0.02$ ) (Table 2, Fig. 3). Responders were 34.78% in the A group and 33.33% in the B one ( $p = 0.477$ ).

Table 2  
Clinical features at the time of randomization and after treatment of the two groups

TREATMENT GROUPS				
		A: ACUPUNCTURE	B:PHARMACOLOGICAL	p value
<b>Headache attacks (number/month)</b>				<b>0.0004<sup>a</sup></b>
T1	<i>mean ± SD</i>	5.72 ± 2.33	5.82 ± 2.12	< <b>0.0001<sup>b</sup></b>
T2	<i>mean ± SD</i>	4.59 ± 2.74	4.23 ± 2.20	0.6679 <sup>c</sup> 0.4668 <sup>d</sup>
<b>Headache days (number/month)</b>				<b>0.0001<sup>a</sup></b>
T1	<i>mean ± SD</i>	8.58 ± 3.21	8.29 ± 2.72	< <b>0.0001<sup>b</sup></b>
T2	<i>mean ± SD</i>	6.43 ± 3.45	6.27 ± 4.01	0.6099 <sup>c</sup> 0.8768 <sup>d</sup>
<b>Number of Medication Intake (number/month)</b>				<b>0.0260<sup>a</sup></b>
T1	<i>mean ± SD</i>	8.17 ± 4.71	8.25 ± 4.27	<b>0.0025<sup>b</sup></b>
T2	<i>mean ± SD</i>	6.34 ± 4.90	6.31 ± 4.54	0.9708 <sup>c</sup> 0.9354 <sup>d</sup>
<b>Legend:</b> <sup>a</sup> : Repeated measures ANOVA; <sup>b</sup> from testing parameters for all patients across time (T1, T2); <sup>c</sup> from testing parameters between groups (A and Non-Responders); <sup>d</sup> from testing the interaction between groups and time of parameters (T1, T2 and Responders and Non-Responders); SD: standard deviation.				
Legend: F: Females; M: Males				

The number of headache attacks decreased significantly after treatment without differences between groups (headache frequency, time-effect:  $p < 0.0001$ ,  $F = 19.03$ ; group effect:  $p = 0.6679$ ,  $F = 0.18$ ; interaction frequency-group effects:  $p = 0.4668$ ,  $F = 0.53$ ) (Table 2, Fig. 3). The number of medication intake decreased significantly after treatment without differences between groups (number of acute medication, time-effect:  $p = 0.0025$ ,  $F = 9.38$ ; group effect:  $p = 0.9708$ ,  $F = 0.00$ ; interaction days-group effects:  $p = 0.9354$ ,  $F = 0.01$ ) (Table 2, Fig. 3).

According to the intention-to-treat analysis: number of migraine attacks decreased after treatment without differences between groups; number of migraine days decreased after treatment without differences between groups; number of acute medications decreased after treatment without differences between groups.

At the end of treatment the satisfaction questionnaire and MIDAS score did not differ between the 2 groups.

Concerning follow-up visit in patients completing the treatment (n = 103), 44 patients (18 randomized to A and 26 to B) interrupted the protocol at T2: 34 (18 randomized to A and 26 to B) need to continue the prophylactic treatment due to the frequency of migraine, 5 (1 randomized to A and 4 to B) preferred to continue their treatment (for other comorbidities as depression, insomnia, etc.), 2 (1 randomized to A and 1 to B) moved to another town and 3 (1 randomized to A and 2 to B) withdrew their consent and refused to continue the protocol. Therefore 59 patients (39 randomized to A and 20 to B) were evaluated at T3. The frequency of attacks/month was  $3.9 \pm 2.4$  (A:  $4.1 \pm 2.5$ , B:  $3.5 \pm 2.3$ ,  $p = 0.4231$ ), the frequency of days/month was  $5.4 \pm 3.5$  (A:  $5.8 \pm 3.5$ , B:  $5.0 \pm 3.5$ ,  $p = 0.5571$ ), and the number of rescue treatment was  $5.7 \pm 5.0$  (A:  $6.3 \pm 4.6$ , B:  $4.6 \pm 3.4$ ,  $p = 0.2243$ ).

At T3 19 patients (9 randomized to A and 10 to B) interrupted the protocol: 15 (7 randomized to A and 8 to B) need the reintroduction of migraine prophylaxis and 4 (2 randomized to A and 2 to B) withdrew their consent and refused to continue the protocol. Therefore 40 patients (30 randomized to A and 10 to B) ended the protocol. The frequency of attacks/month was  $3.7 \pm 2.1$  (A:  $4.1 \pm 2.3$ , B:  $2.6 \pm 1.4$ ,  $p = 0.0685$ ), the frequency of days/month was  $4.8 \pm 2.6$  (A:  $5.2 \pm 2.5$ , B:  $3.7 \pm 2.8$ ,  $p = 0.1297$ ), and the number of rescue treatment was  $4.6 \pm 2.9$  (A:  $5.0 \pm 2.9$ , B:  $3.4 \pm 2.9$ ,  $p = 0.1769$ ). The two groups did not differ for scores at Zung scales, MIDAS and SF-36 both at T3 and T4 visits.

On the total sample completing the treatment, the 33.0% and 25.4% required prophylaxis therapy after 3 and 6 months respectively, with an higher proportion in patients randomized to B group (n = 19/46, 41.3% after T2; n = 8/46, 17.4% after T3) than those randomized to A group (n = 15/57, 26.3% after T2; n = 7/57, 12.3% after T3).

The improvements observed at the end of treatment persisted after therapy in 57.3% (59/103) after 3 months (T3) and in 38.8% (40/103) after 6 months (T4), especially in patients randomized to acupuncture treatment (68.4% at T3 and 52.6% at T4 in A group; 43.5% at T3 and 21.8% at T4 in B group).

## Discussion

This study suggests that in a population of patients with episodic migraine, acupuncture was as effective as pharmacological treatment in decreasing migraine frequency. The migraine days in a month decreased significantly after treatment, without differences between the two groups. In the same way, migraine attacks and number of acute medication significantly decreased after treatment without

differences between the two groups. Moreover, in our trial, about 34% of patients showed a reduction of headache days by at least 50% after the treatment.

The analysis of our sample resulted in the further following clinically relevant suggestions: a) the 15.5% of patients (21/135) interrupted the treatment, especially those randomized to pharmacological drugs; b) the improvements observed at the end of treatment persisted in 57.3% (59/103) after 3 months and in 38.8% (40/103) after 6 months, especially in patients randomized to acupuncture treatment; c) the 33.0% and 25.4% required prophylaxis therapy at 3 and 6 months follow-up visits.

First, our results are in line with previous studies on the effectiveness of acupuncture to standard pharmacologic treatment showing acupuncture to be “at least non-inferior” to conventional treatments in episodic migraine [8–10]. However, methodological heterogeneity precludes aggregation of these data and impacts comparison among studies [9–10]. Six previous studies compared acupuncture with pharmacological treatments in episodic migraine [11–16]. In the first randomized study 85 patients, with migraine with and without aura, were allocated to a 17-week regimen either with acupuncture and placebo tablets or to placebo stimulation and metoprolol 100 mg daily: both group exhibited a reduction in attack frequency while metoprolol group showed a lower global rating of attacks [11]. In a more recent randomized controlled multicentre trial, 114 migraine patients were randomized to treatment over 12 weeks either with acupuncture (8 to 15 sessions) or metoprolol (100 to 200 mg daily). The number of migraine days decreased in both group and the proportion of responders (reduction of migraine attacks by  $\geq 50\%$ ) was 61% for acupuncture and 49% for metoprolol [16]. One randomized controlled trial on 160 women with migraine compared acupuncture (n = 80) with flunarizine (n = 80) over 6 months founding that frequency of attacks and use of symptomatic drugs significantly decreased during treatment in both groups, with a lower migraine frequency after 2 and 4 months in the acupuncture group than in pharmacological one [12]. More recently, a multicentre, double-dummy, single-blinded, randomized controlled trial recruited and assigned 140 patients with migraine without aura to 2 different groups: the acupuncture group treated with verum acupuncture plus placebo and the control group treated with sham acupuncture plus flunarizine. This study suggested that acupuncture was more effective than flunarizine in decreasing days of migraine attacks, whereas no significantly differences were found between the two groups in reduction of pain intensity and improvement of quality of life [13].

Another trial performed in 100 patients with migraine without aura, 50 patients randomized to acupuncture and 50 to Valproic acid treatment, during a 6-months follow-up, reported an improvement on MIDAS score during the follow-up in both group and an improvement on pain intensity and pain relief score in acupuncture group at 6-month visit [14].

Only one prospective, multicentre, double-blind, parallel-group, controlled, clinical trial randomized 960 patients to verum acupuncture (n = 313), sham acupuncture (n = 339), or standard therapy (n = 308): the improvement in the number of migraine days was closely similar in all treatment groups [15].

Second, concerning adverse events and compliance of treatment, the 15.5% of patients (21/135) interrupted the treatment (6 patients randomized to acupuncture and 15 to pharmacological prophylaxis).

Despite there were not differences in patients preference for acupuncture or pharmacological treatment between the two groups at the time of enrollment, patients allocated to pharmacological treatment more frequently interrupted the therapy. In particular, in pharmacological group 7 patients withdrew their consent for study participation directly after randomization, 2 showed mild adverse event to drugs and 6 showed a poor compliance while in acupuncture group 4 did not tolerate acupuncture and 2 showed a poor compliance. These data suggested that acupuncture showed less side effect and a higher compliance than pharmacological therapy. Our findings are partially similar to those reported in previous studies. A systematic review published by the Cochrane Library in 2016 found moderate evidence favoring acupuncture over conventional treatment for safety and tolerability, given that acupuncture produced a lower number of pooled adverse effects and had a lower likelihood of dropouts [9]. However, previous trials reported a high proportion of participants allocated to drug treatment who withdraw informed consent immediately after randomization (8% [14], 13% [16] and 34% [15]), an high treatment discontinuation (18% [15]) and dropout rates due to adverse effects (9% [12] and 16% [16]). Compared to other studies, the lower rate of informed consent withdraw after randomization (10.6%), as well as of treatment discontinuation (9.1%) and of dropout due to adverse events (3.0%) in our sample, is probably due to the involvement of patients in the choice of the best medical treatment on the basis of their comorbidities (i.e. depression, insomnia, overweight, hypertension, etc.), previous migraine prophylaxis and their preference to nutraceutical treatment, as in clinical practice [4–6]. Moreover, the higher compliance in acupuncture group could be also ascribable to a closer follow-up received from patients allocated to acupuncture than those allocated to pharmacological treatment who were evaluated once after 4 months of therapy with a telephone interview after 2 months of treatment. Moreover, in our eligible sample, a large proportion of patients declined to participate at the time of enrolment because they would refused acupuncture treatment (n = 31/39, 79.4% ) respect to those who refused the pharmacological treatment (n = 3/39, 7.7%).

Third, the 33.0% and 25.4% required prophylaxis therapy during the follow-up, especially those randomized to pharmacological treatment. Finally, the improvements observed at the end of treatment persisted after treatment in 57.3% (59/103) after 3 months and in 38.8% (40/103) after 6 months, especially in patients randomized to acupuncture treatment. These data suggested that acupuncture could show a prolonged benefit also after session suspension. However, despite an higher dropout rate in pharmacological group, at 6-months follow-up visit, patients randomized to conventional treatment showed a lower migraine frequency and acute medication intake without reaching a significant difference. Few studies focused of follow-up efficacy after the end treatment. The study performed by Wang et al. demonstrated that the prophylactic effects of both acupuncture and flunarizine persisted from the end of the treatment through the next 3 months, and verum acupuncture was slightly better than flunarizine in term of responders proportion (59% vs 40% after 4 weeks and 56% vs 37% after 16 weeks) and mean reduction of migraine days (4.1 vs 1.9 days after 4 week and 4.1 vs 2.0 days after 16 week) [13]. One study compared valproate and acupuncture showing that both therapies were effective at 3 and 6-months follow-up in relieving migraine as regards severity of attacks, disability, intensity of pain and rizatriptan intake. Valproate provides a better control of pain at 3 months, while acupuncture is superior

at 6-months [14]. Similar findings were reported in another study, comparing verum acupuncture with standard drugs after 6 weeks of treatment, in whom the responders were significantly higher in the verum acupuncture group (52%) than in the standard drug group (39%) at week 6, without differences between the 2 groups at week 26 (47% in verum group, 40% in standard group) [15]. Therefore, further studies on larger sample and with a standardized analysis of migraine frequency, adjusted from therapy and other confounding factors, should be performed to better investigate benefit after treatment suspension.

Finally, future researches should be performed to compare acupuncture with the emerging anti-CGRP monoclonal antibodies, which have shown comparable efficacy with currently available oral agents for migraine prevention but superior safety and tolerability profiles.

Strength of our study were the semi-structured acupuncture session, the standardized acupuncturist training, the comparison of acupuncture with the best prophylactic drugs for patients taking into consideration comorbidities (i.e. depression, insomnia, hypertension etc.) and previous preventive treatment which probably contribute to improve the compliance and to reduce adverse events.

Several limitations of our study should be discussed. First of all, this was an open study and the lack of blindness of patients and neurologists could impact the compliance: patients randomized to acupuncture received a closer follow-up while patients randomized to pharmacological treatment were evaluated once after 4 months of therapy. However, we would like to investigate the efficacy of acupuncture in comparison to routine care, choosing the best medical treatment for each patient, as in real-life clinical practice, and for these reasons we did not take into consideration a study design including sham acupuncture [15, 21–23]. The sample size is relatively small but for feasibility reasons in our neurological ward, we did not recruit further patients.

Finally, the enrollment in tertiary Headache Centres, probably contributed to select patients who preferred traditional treatment but, on the other side, this allows to not include only subjects with a high expectation for non-conventional treatments.

## Conclusion

Our trial is the first one comparing acupuncture with the more appropriate pharmacological treatment for migraine prophylaxis. Data suggested that acupuncture could be adopted as a migraine prophylaxis and seem to be slightly superior to pharmacological treatment in compliance and rate of adverse events. However, clinicians should consider that, in our setting, a large proportion of patients refused acupuncture for time restriction, distance problems, phobia or preference for standard therapy.

## Abbreviations

Group A

Acupuncture; Group B: pharmacological group; MIDAS: Migraine Disability Assessment Score; SF-36: 36-Item Short-Form Health Survey;

# Declarations

## **Ethics approval and consent to participate**

The study was conducted in agreement with principles of good clinical practice and the study protocol was approved by the Local Ethic Committee of the local health service of Bologna, Italy (n. 09002). All patients gave their written informed consent to study participation.

## **Availability of data and materials**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

## **Competing interests**

None of the authors has any conflict of interest to disclose for this study.

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## **Authors' contributions**

Giulia Giannini: acquisition, analysis and interpretation of data, drafting the manuscript.

Valentina Favoni: acquisition and interpretation of data

Elena Merli: acquisition and interpretation of data

Marianna Nicodemo: acquisition of data

Paola Torelli: acquisition and interpretation of data, critical revision of the manuscript

Annunzio Matrà: acquisition and interpretation of data

Carlo Maria Giovanardi: acquisition and interpretation of data, critical revision of the manuscript

Pietro Cortelli: substantial contributions to conception and design of the study, critical revision of the manuscript.

Giulia Pierangeli: substantial contributions to conception and design of the study, critical revision of the manuscript.

Sabina Cevoli: conception and design of the study, acquisition and interpretation of data, supervision of the study, critical revision of the manuscript.

All authors read and approved the final manuscript.

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## Figures

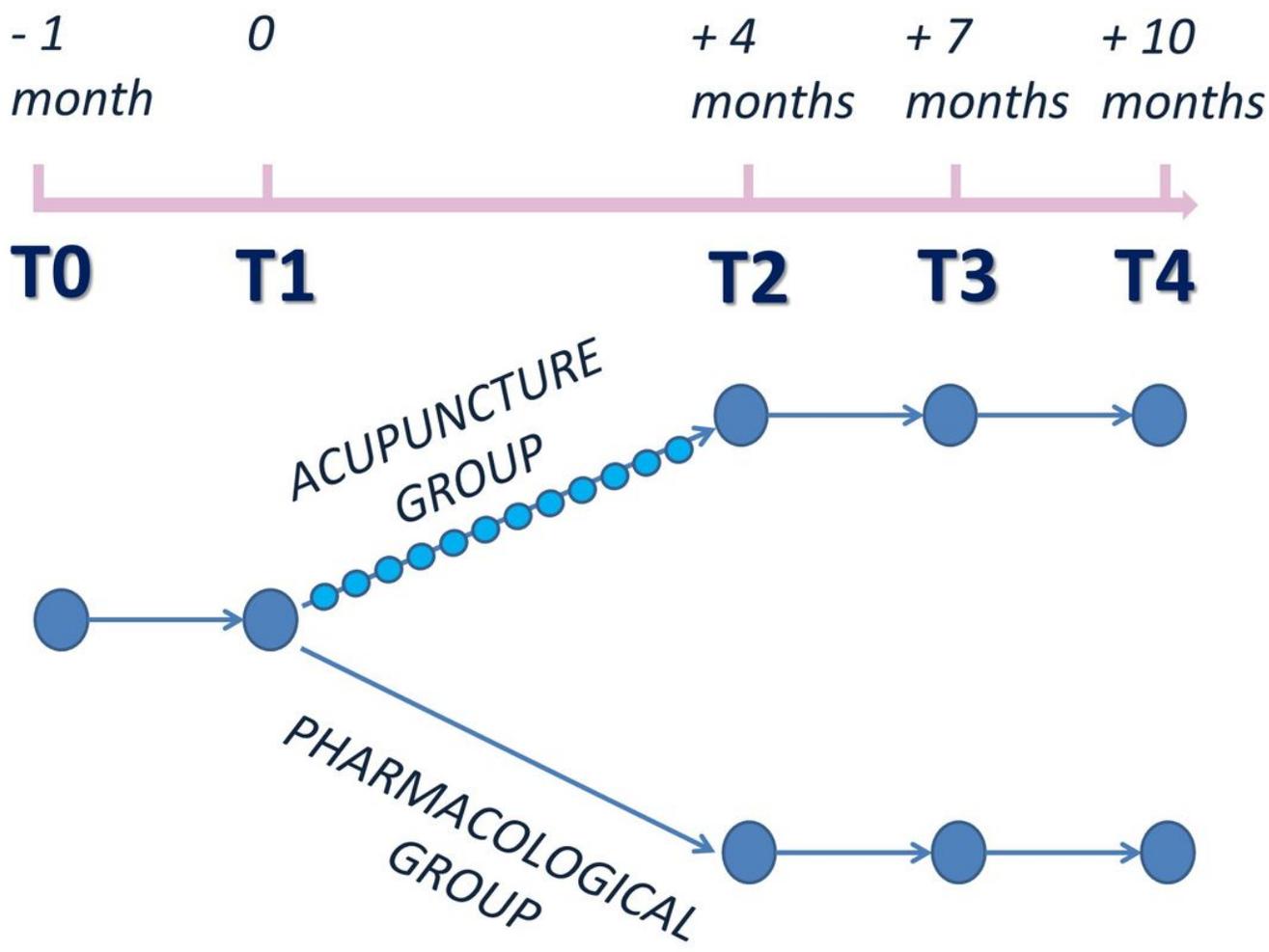
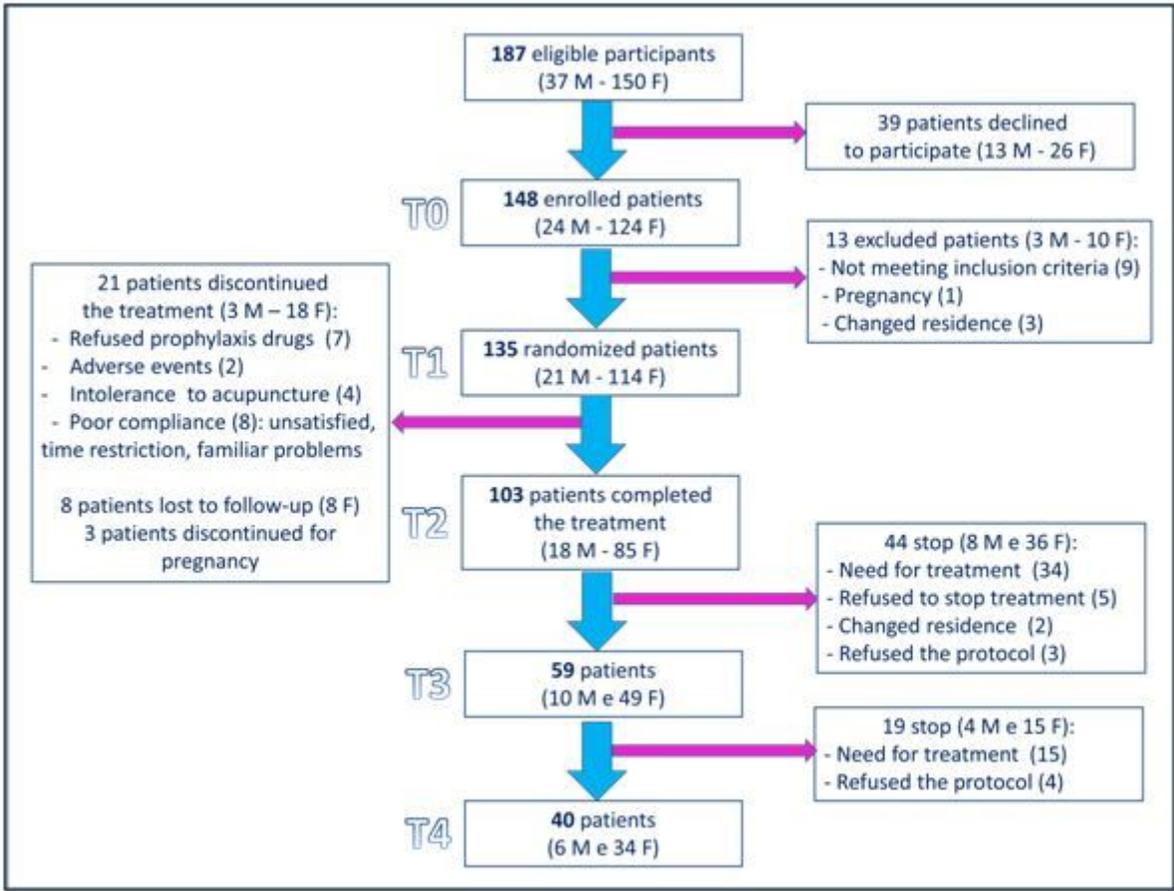


Figure 1

Study Design



Legend: F: Females; M: Males

Figure 2

Study flow-chart

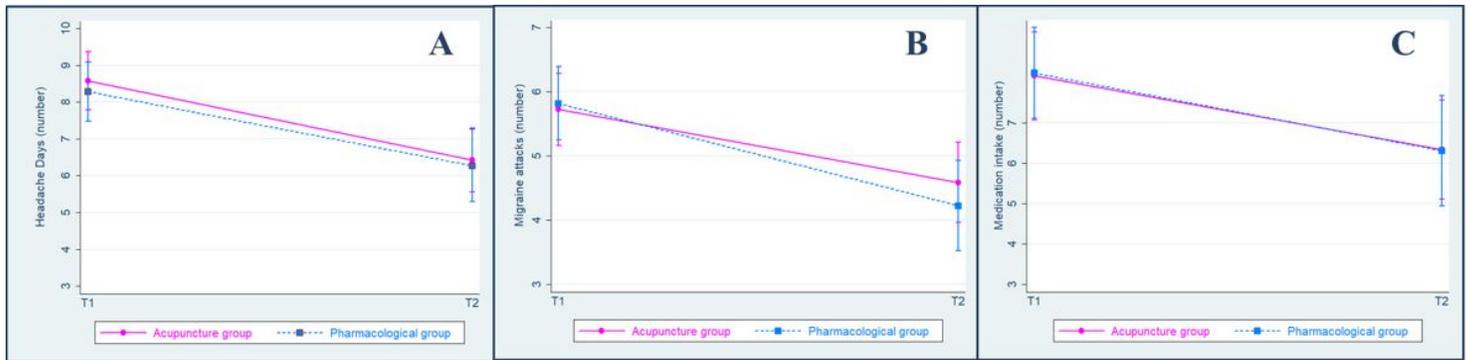


Figure 3

Adjusted Predictions of interaction between time (T1 and T2) and groups (Acupuncture and Pharmacological groups) on parameters with 95% CIs