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Clinical trial

Effect of expectation on short- and long-term treatment response to Acupuncture in migraine patients

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ABSTRACT

Introduction: There are relatively few studies addressing the relationship between the patient's expectation and the short and long-term response to treatment with acupuncture. The aim of this study was to assess the association between pre- and post-treatment expectation of acupuncture and post-treatment and post-follow-up patient outcomes.

Methods: This was an open-label, randomized controlled clinical trial conducted at the Czech-Chinese Centre for Traditional Chinese Medicine at the University Hospital Hradec Kralove between October 2015 and April 2017. Non-specific factors were examined in the intervention arm using regression analysis.

Results: Post-treatment positive expectation concerning the success of the treatment, as well as the affective status of the patient, is one of the most significant nonspecific factors contributing to an increased post-treatment effectiveness of acupuncture; however, this positive expectation decreased with time. On the other hand, the post-follow-up effect of acupuncture was significantly improved by the patients' positive perception of the TCM practitioner.

Conclusions: Correct calibration of a patient's expectation, good mental status, and patients' perceptions of an acupuncturist's skills reduced the number of migraine days in patients treated with acupuncture. Understanding non-specific treatment effects can potentially help clinicians to integrate them in to practice and thus optimise treatment effectiveness. Future research is needed to clarify whether interventions targeting modifiable non-specific factors prior to and during acupuncture treatment can result in better patient outcomes and future cost-savings.

1. Introduction

With a prevalence of 18–25 % in females and 6–8 % in males, migraine has become a major health problem [1,2]. In the European Union alone, the average annual costs of migraine treatment in adults approximate ˜€1222 per person [3,4]. In the United States, average annual costs per patient amount to ˜$1757 according to the American Migraine Prevalence and Prevention [1,3,4]. Because of the suboptimal effect of pharmacological treatments [5,6], up to 41.3% of migraine patients often turn to complementary and alternative medicines (CAM) such as Acupuncture [7–9]. The review on acupuncture for the prevention of episodic migraine by Linde et al. concluded that adding acupuncture to the symptomatic treatment of attacks reduces the frequency of headaches and as such may be at least similarly effective as treatment with prophylactic drugs [10]. CAM approaches often derive effects on the general health and well-being of patients from a whole system of care, which typically encompasses a number of so-called nonspecific factors in addition to the putative specific, or active, ingredient (in acupuncture the specific ingredients would include the action of the needles and other therapeutic interventions based on the

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underlying theory of acupuncture) [10–14] In particular, patients commencing acupuncture, and other forms of CAM, may have a set of expectations based on the offered treatment, their specific disease, experience with previous treatments and physicians, as well as other factors such as age, gender, education, marital status [15,16]; while additional non-specific factors that might contribute to the effects of acupuncture include the character of the therapist, the context of therapy, and the relationship between the patient and the physician and their mutual empathy [17–19].

The placebo response rate in the treatment of acute headache episodes were reported to be higher than in headache prophylaxis; and invasive procedures, such as injections, had a higher placebo response when compared with orally administered drugs [20–26]. In the case of acupuncture, the placebo effect in the treatment of pain was considered as mild [10]. Nevertheless, there are some "pill versus needle" studies suggesting needles outperforming pills. [27]. In the case of migraine, there are relatively few studies addressing the relationship between the patient's expectation and the short and long-term response to treatment with acupuncture [28]. Linde et al., who primarily evaluated the efficacy of real *vs*. placebo acupuncture in patients suffering from migraine, tension headache, chronic back pain, and osteoarthritis, concluded that the results were dependent not on the acupuncture treatment but rather on patients' own expectations [10]. Nevertheless, a negative correlation between a positive expectation by the patient and a higher acupuncture efficacy were observed in some studies [28,29]. This paradoxical finding was explained by the authors by stating that patients with higher expectation could be more disappointed by their results than those who undergo acupuncture without expecting positive results [19]. This hypothesis can be supported by the results of another study by Zhang et al., which monitored the effect of pre- and post-treatment expectation on the number of migraine days, finding that the result of the treatment was determined by the expectation of the patients after treatment rather than prior to its beginning [30]. Thus, expectation seems to be primary source of the placebo effect [24,25], which may change during the course of treatment and afterwards [30,31]. In a study by Musil et al, a statistically significant difference was observed in reduced symptoms and medication use in migraine patients in the acupuncture vs waiting-list control groups both at the end of the intervention as well as at the 6-month follow up [32]. The aim of the present study was a secondary analysis of those migraine patients in the acupuncture group to assess the expectation and other non-specific factors using validated instruments and to identify the most powerful non-specific elements leading to positive patient outcomes after 12-week acupuncture and at a 6-month follow-up.

2. Methods

2.1. Patients

A sample population of 42 patients in the acupuncture treatment arm was selected from the original dataset of 91 patients for the secondary analysis [33]. Ninety-one patients between 18 and 70 years of age attending the neurology outpatient clinic at the University Hospital Hradec Kralove were consecutively enrolled in this study; such patients had to be diagnosed with migraine with or without aura by board-certified neurologists according to the criteria of the International Classification of Headache Disorders and suffer from more than four migraines a month for at least 12 months in order to participate in the study [33]. Patients were randomized (each block consisted of 12 participants) to either a 12-week treatment with acupuncture or a waiting-list control group based on age, sex and disease severity. An independent researcher prepared the computer-generated randomization. All patients used standard pharmacological treatments. The clinical trial was not double blinded. The evaluation of the treatment procedure and efficacy have been described in detail elsewhere [32]. All patients who were randomized in the original clinical study to receive acupuncture treatment in addition to their pharmacological treatment were selected for the secondary analysis in this study. All patients signed a written informed consent prior to filling in the questionnaires during the baseline period (September, 2015 – August, 2016). The study was approved by the Ethical Committee of the University Hospital Hradec Kralove (Ref.No.67 P).

2.2. Outcome measures

The objective was to measure the association between pre- and post-treatment expectation of the treatment and its outcome. Patient outcomes were defined as (a) the number of migraine days and (b) the reduction in relief medication use during the last 4 weeks before randomization (baseline period) and weeks 12 and 36 after randomization. Information on the number of migraine days as well as relief medication use was collected from the patients' personal log as described previously [32].

2.3. Expectation

Patient expectation concerning the outcome of the treatment was measured by the 3-item expectation subscale (EQ) of the Credibility and Expectation Questionnaire (CEQ) by Devilly and Borkovec [34,35]. Patients were asked about how they feel and how they think their migraine will improve due to acupuncture. They supplied their filled questionnaires to the study's nurses, who assured the questionnaire would not be reviewed by either their conventional physician or TCM practitioner. The patients filled the EQ before the treatment (prior randomization), after 12-week acupuncture treatment (post-treatment expectations) and at the 6-month follow-up (post-follow-up expectations) (Fig.1).

The CEQ possesses a high internal consistency (a = 0.79–0.90) and high retest reliability (r = 0.82) concerning the expectation factor [35]. The CEQ was translated into Czech language by two independent persons and piloted with a diverse sociodemographic subset of patients with mild to severe migraine. The EQ items were standardized due to the different character of scales [*e.g.* scale from 0 (not at all) to 10 (very

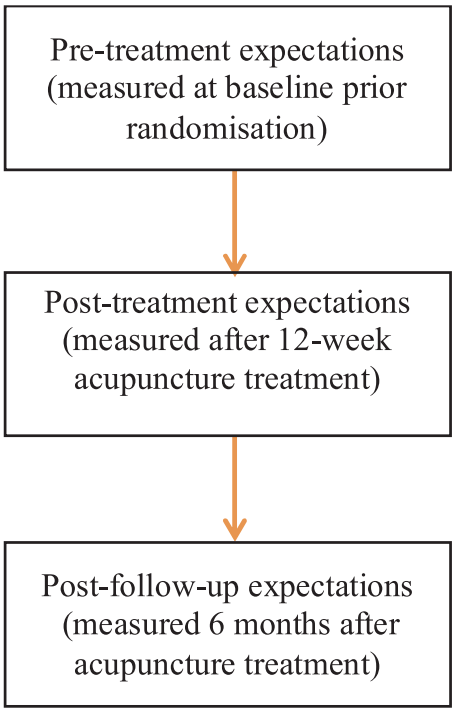

Fig. 1. A flowchart of measurement points of patients expectations measured by the Expectancy Subscale of the Credibility and Expectancy questionnaire.

much), and 0% (not at all) to 100% (very much)]; the sum score ranged from 0 to 30.

A battery of standardized questionnaires was distributed to the subjects to assess their outcome as well as confounding factors before the treatment (prior randomization), after 12-weeks of acupuncture and at the 6-month follow-up: depression and anxiety (Symptom Check-list 90 Subscales, SCL-90) [36], the patient-physician relationship (The Consultation and Relational Empathy Measure, CARE) [19], and migraine disability (Migraine Disability Assessment Scale, MIDAS) [37]. Further, the patients were asked a set of questions using visual analogue scales (VAS) [38], regarding other potentially confounding factors: belief in complementary medicine (VAS, 0 = not at all, 10 = fully believe), prior experience with acupuncture (VAS, 0 = negative experience, 10 = positive experience), fear of needles (VAS, 0 = not at all, 10 = strongly fear), satisfaction with acupuncture (VAS, 0 = unsatisfied, 10 = satisfied), De qi sensation (1 = yes/0 = no), migraine occurrence expectation (VAS, 0 = not at all, 10 = very often), and patients' perceptions of an acupuncturist's skills (VAS, 0 = poor skills, 10 = excellent skills) prior study initiation. Sociodemographic data such as age, gender, education, religion, income, and disease duration were collected as well.

2.4. Statistical analysis

Variable normality was determined using the Kolmogorov-Smirnov test (K–S). To identify the non-specific predictors of treatment outcomes, linear regression analysis was used. The difference in the number of migraine days and the difference in drug consumption after 12-week acupuncture and a 36-week follow-up were considered the dependent variables in the multiple linear regression, respectively. A univariate linear regression was computed for non-specific factors given in Table 2. The only parameters that appeared to be statistically significant were entered into multivariate linear regression analysis as input variables. Confounding factors were selected with regards to the purpose and character of the study; these included age, gender, education, religion, disease duration, migraine disability, anxiety, depression, pre/post-treatment expectation, belief in complementary medicine, prior experience with acupuncture, fear of needles, satisfaction with acupuncture, De qi sensation (a composite of unique sensations acting as a prerequisite for clinical effects), migraine occurrence expectation, relationship between the patient and their physician or TCM practitioner, and patients' perceptions of an acupuncturist's skills [18,20].

A sensitivity analysis was conducted for determining of the effect size of the regression model: F-test for multiple linear regression, fixed model, R2 deviation from zero with parameters with $\alpha = 0.05$, power $(1\text{-}\beta) = 0.8$. All conducted tests were two-sided. All patients with missing values in concrete analysis were removed from the analysis. The power was determined using the G*power tool. The statistical analysis was performed using the software SPSS version 18.0 ($p \leq 0.05$).

3. Results

The baseline characteristics of the patients and their psychosocial profile are shown in Tables 1 and 2.

3.1. Effect of expectation on the number of migraine days

3.1.1. Post-treatment effect (at the end of acupuncture treatment)

Multiple linear regression for the number of migraine days at the end of acupuncture treatment was computed in unadjusted ($R^2 = 0.52$, $F(5,26) = 5.60$, $p < 0.001$), and adjusted ($R^2 = 0.64$, $F(9,22) = 4.83$, $p < 0.001$) versions. Significant negative associations were found with fear of needles (B = -0.4, 95% CI -0.7 to 0.0, p = 0.033) and positive associations with the patients' post-treatment expectation of migraine and the level of depression (B = 1.0, 95% CI 0.4–1.7, p = 0.004). These relationships were found significant even after adjustment (Table 3). No other factors such as the pre-treatment expectations were found significant. Sensitivity analysis for adjusted model with input parameters $\alpha = 0.05$, $(1\text{-}\beta) = 0.8$, 9 predictors and sample size n = 37 determines critical F = 2.25. Value F of our adjusted model is F = 4.83 > critical F, therefore model fulfilled defined assumptions.

It must be noted that in this interpretation the dependent variable is considered as a difference. Positive difference indicates a greater occurrence of migraine days after 12-week of acupuncture or the 36-week follow-up, i.e. an undesirable state. On the other hand, the negative difference of the dependent variable indicates fewer number of migraine days, i.e. a desired state.

3.1.2. Post-follow-up effect (6-month follow-up)

Multiple linear regression for the number of migraine days at the follow-up was again computed in unadjusted ($R^2 = 0.25$, F

Table 1
Sociodemographic characteristics of respondents (N = 42).

		N	%
Overall		42	100.0
Gender			
	Male	5	11.9
	Female	37	88.1
Age			
	up to 29 years	6	14.3
	30-39 years	6	14.3
	40-59 years	24	57.1
	60 years and more	6	14.3
Education			
	Less than high school	1	2.4
	High school	27	64.3
	University	14	33.3
Monthly household income in CZK [a]			
	< 10.000	2	4.8
	10.001 – 20.000	4	9.5
	20.001 – 40.000	22	52.4
	> 40.001	14	33.3
Religious identity. n (%)			
	Atheist	32	76.2
	Churchman	10	23.8
Duration of migraine, years, mean (SD)		26.9	(12.9)
Drug consumption, (ATC/DDD), mean (SD)		14.8	(14.3)

CZK. Czech Crowns

[a] 1 EUR = 24.58 CZK (2015).

Table 2
Baseline characteristics of non-specific factors (n = 42).

	Mean(SD)	Med	(Min, Max)
Post-treatment expectancy (EQ)	18.8 (7.3)	19.0	(0.0, 30.0)
Pre-treatment expectancy (EQ)	23.6 (4.0)	24.0	(14.3, 30.0)
Disease duration	26.9 (12.9)	27.5	(2.0, 50.0)
Depression (SCL-D)	0.9 (0.6)	0.8	(0.2, 2.2)
Anxiety (SCL-U)	0.6 (0.5)	0.4	(0.1, 2.0)
Belief in complementary therapies like acupuncture	6.9 (2.0)	7.0	(0.3, 10.0)
Prior experience with acupuncture	0.4 (0.6)	0.0	(0.0, 3.0)
Fear of needles	2.4 (3.1)	2.0	(0.0, 10.0)
Prior satisfaction with acupuncture	8.1 (1.7)	8.0	(5.0, 10.0)
Migraine occurrence expectancy	4.9 (1.9)	5.0	(1.0, 10.0)
TCM professionalism assessment	9.8 (0.4)	10.0	(8.5, 10.0)
De qi sensation, n (%)	80.0 (40)	100.0	(0.0, 100.0)
CARE (patient-western physician)	45.5 (5.2)	47.0	(32.0, 50.0)
CARE (patient-TCM physician)	45.4 (5.6)	47.0	(28.0, 50.0)

EQ; Subscale of the Expectancy and Credibility Questionnaire, CARE; The Consultation and Relational Empathy measure, SCL-A; Anxiety subscale of the Symptom Check-list, SCL-D; Depression subscale of the Symptom Check-list, TCM; Traditional Chinese Medicine.

Table 3
Multiple variables linear regression analysis for the associations between non-specific factors and reduction in the number of migraine days after 12-week acupuncture treatment (N = 37).

	Unadjusted		Adjusted [b]	
	sig.	B(CI)	sig.	B(CI)
(Constant)	0.163	−8.0 (-19.5; 3.5)	0.466	−4.6 (-17.6; 8.3)
Gender			0.371	−1.5 (-5.0; 2.0)
Age			0.311	−0.7 (-2.2; 0.7)
Education			0.206	−1.4 (-3.6; 0.8)
Religious identity			0.097	−2.2 (-4.7; 0.4)
Post-treatment expectancy (EQ)	0.007	−0.3 (-0.4; -0.1)	0.002	−0.3 (-0.5; -0.1)
Depression (SCL-D)	0.029	2.4 (0.3; 4.5)	0.004	3.6 (1.3; 5.9)
Fear of needles	0.042	−0.4 (-0.8; 0.0)	0.033	−0.4 (-0.7; 0.0)
Migraine occurrence expectancy	0.009	0.9 (0.2; 1.5)	0.004	1.0 (0.4; 1.7)
The Consultation and Relational Empathy (Care)[a]	0.665	0.1 (-0.2; 0.3)	0.338	0.1 (-0.1; 0.3)

EQ; Subscale of the Expectancy and Credibility Questionnaire, CARE; The Consultation and Relational Empathy measure, SCL-A; Anxiety subscale of the Symptom Check-list, SCL-D; Depression subscale of the Symptom Check-list, TCM; Traditional Chinese Medicine.

CARE; [a]The Consultation and Relational Empathy measure between the TCM physician and patient, SCL-D; Depression subscale of the Symptom Check-list [b]A univariate linear regression was computed for non-specific factors given in Table 2. The only parameters that appeared to be statistically significant were entered into multivariate linear regression analysis as input variables.

Table 4
Multiple variables linear regression analysis for the associations between non-specific factors and reduction in the number of migraine days at a 6-month follow-up (N = 37).

	Unadjusted		Adjusted [a]	
	sig.	B(CI)	sig.	B(CI)
(Constant)	0.077	27.4 (-3.1; 57.9)	0.066	29.9 (-2.1; 61.8)
Gender			0.218	−2.6 (-6.8; 1.6)
Age			0.288	0.9 (-0.8; 2.7)
Education			0.35	−1.5 (-4.7; 1.7)
Religious identity			0.15	−2.4 (-5.7; 0.9)
Belief in complementary therapies like acupuncture	0.039	0.7 (0.0; 1.4)	0.026	0.8 (0.1; 1.6)
TCM professionalism assessment	0.014	−4.0 (-7.1; -0.9)	0.016	−4.0 (-7.1; -0.8)

[a] A univariate linear regression was computed for non-specific factors given in Table 2. The only parameters that appeared to be statistically significant were entered into multivariate linear regression analysis as input variables.

(2,31) = 5.16, p = 0.012), and adjusted (R^2 = 0.60, F(6,27) = 2.49, p = 0.048) versions. Higher patients' perceptions of an acupuncturist's skills had positive impact on treatment outcome and led to decreased number of migraine days (B = -4.0, CI -7.1 to -0.8, p = 0.016). In contrast, belief in complementary medicine such as acupuncture increased number of migraine days (B 0.8, CI 0.1–1.6, p = 0.026). Both variables remained significant after adjustment (Table 4). *Sensitivity analysis for adjusted model with input parameters α = 0.05, (1-β) = 0.8, 9 predictors and sample size n = 37 determines critical F = 2.42. Value F of our adjusted model is F = 4.49 > critical F, therefore model fulfilled defined assumptions.*

3.2. Effects of expectation on post-treatment and post-follow-up drug consumption

Any non-specific factor was not significantly associated with more than a 50% reduction in medication consumption after 12-week acupuncture.

At 36-week follow-up, belief in complementary medicine such as acupuncture and patients' perceptions of an acupuncturist's skills led to more than a 50% reduction in medication consumption; nevertheless, neither of the factors remained significant in the final adjusted model.

4. Discussion

The aims of the present study were to evaluate non-specific factors in the acupuncture treatment of migraine patients and to identify the most powerful non-specific components leading to positive outcomes after a 12-week acupuncture course and at a 6-month follow-up.

Our study showed that the patients had higher expectations after than before acupuncture therapy, reporting a decreased number of migraine days during the last 28 days of treatment. Our results are consistent with previous studies where post-treatment expectations (at the end of acupuncture treatment) were found to be a significant predictor of improved patient outcomes [31]. On the other hand, we could not confirm the finding that higher pre-treatment expectations resulted in better health for the patients [39–43]. The relationship between the expectations and patient outcomes thus appears to be more complex. The general improvement of symptoms during the course of acupuncture therapy leads to higher expectations of treatment efficacy, which, in turn, influences the positive effect of the treatment itself. It can be said that in the course of acupuncture treatment, the expectations of treatment efficacy and the real therapeutic effect are gradually re-calibrated to an optimal level; here calibration means minimizing the difference between the subjective evaluation and the real therapeutic effect, *i.e.* real (achievable) expectations of a decrease in the number of migraine days and improvement of the symptoms. The re-calibration of the expectations influences the patient's satisfaction or disappointment with the treatment. Moreover, the patients' expectations reflect their motivation and willingness to comply with the treatment, which, in turn, influences their compliance. Gradual re-calibration to a correct level of expectations improves the patients' attitude to the treatment and willingness to continue acupuncture therapy. However, it is still not clear whether we need to “re-calibrate” the patient from the very beginning of therapy or whether we should rather wait until the patient gets their own experience with acupuncture. The adjustment of expectations, in particular during the follow-up period, seems to be a significant predictor of treatment success by itself [29,31,44,45].

Furthermore, anxiety, depression, or fear of needles, among other factors, was correlated with and may have influenced the post-

treatment efficacy of acupuncture. Whether the patient's tendency towards anxiety and depression influences the occurrence of migraines or, conversely, whether headaches play a role in the development of psychiatric/psychological problems should be considered [46–49]. It can be assumed that a patient expecting the onset of migraine becomes anxious because of the anticipation of migraine [48,50–52]. In our study, the anticipation of migraine was correlated with the actual occurrence of migraine days, as also observed by others [11,43,53]. It implies that the "re-calibration of expectations", which seems to be a predictive factor for better outcomes, will also be influenced by the affective status of the patient. In our study, the fear of needles experienced by the patients prior to the acupuncture treatment was associated with a reduction in the number of migraine days at the end of the treatment. The perception of needles itself may exert a positive placebo effect because patients can perceive the introduction of needles as a significantly more intrusive therapeutic intervention than *per os* medication [28,54,55]. Thus, fear of needles involves a number of other complex constructs at the cognitive level, where emotions as well as the physiological (reflexive) response of the patient influence the total effect of acupuncture. It is also possible to consider the dynamics between the fear of needles and the improved condition of patients after treatment in correlation with their personal experience. The initial fear of needles disappeared on treatment, which could also influence the effect. The deteriorating condition of the patient indicates that, under depression, the effect of needles does not help and expectations are subjectively unfulfilled. Thus, it seems that the assessment of patients' mental status prior to treatment is of high relevance. If depression or anxiety experienced by the patient is decreased by means of psychotherapy before treatment, it is possible to assume that the efficacy of acupuncture will be increased. Therefore, it is important to change the patient's cognitive patterns by means of psychotherapy. A combined effect of education and stress management strategies has previously been confirmed in migraine sufferers [56]. As opposed to psychotropic drugs, psychotherapy addresses the root of the problem and is not being limited to symptoms only, while also exerting minimal side effects.

There was a significant relationship between higher patients' perceptions of an acupuncturist's skills at post-follow-up and the alleviation of migraine symptoms. A similar result has also been shown in other studies [18,20,40,57]. However, the perception of medical care itself did not show statistical significance regarding the treatment effect. The physician–patient relationship is, from a standpoint of the therapeutic effect, more important than the patient's attitude to medical methods as such. Therefore, it can be presumed that putting more hope in an alternative therapy evidently means a certain disappointment to patients. It is possible to see a parallel between hope in alternative therapeutic methods and confidence in conventional medication. If the patient perceives acupuncture in an identical manner to the use of a pill, *i.e.* more as a passive receiver, he/she is most probably disappointed, as a more active attitude of the patient is expected in CAM. We also assume that the expectations of depressive and anxious patients will not correlate with their real inner adjustment. The effect of treatment fails most probably when confronted with the proclaimed expectations and refusal.

Our study has also demonstrated that religion, age, gender, education, number of inhabitants in the region, and illness duration were not correlated with acupuncture effects. However, the research cohort showed a markedly higher representation of women, middle-aged persons (40–59 years), and a moderately higher representation of single people. No relationship was noted between improved expectations (re-calibration) and a decreased use of relief medication in either post-treatment or post-follow-up acupuncture treatment. The patients may use medication as they have been accustomed to, or in a preventive manner, in connection with the anticipation of symptoms and fear of pain. In the course of time, patients may discover that they do not need medication, and their consumption of medicines may decrease in a post-follow-up.

The advantages of the present study are the use of a validated and reliable instrument to assess the patient's expectations and the prospective evaluation of a range of non-specific confounding factors as well as post-treatment and post-follow-up outcomes. On the other hand, the statistical significance of these relations may not be observed in a secondary analysis of the data with regards to the reported medium effect size. Though the evaluation of expectations is devoted mainly to patients, several studies have demonstrated that even physicians may have their own set expectations and thus unconsciously influence the course of treatment [7,58–61]. Such factors are difficult to control; nevertheless, the physicians were instructed to approach all patients equally throughout the study. However, we did not measure the physicians' expectations. Also, the inclusion criteria of the clinical trial [32] may limit the generalisability of the study findings to other settings and patients with less severe migraine. A larger trial is desirable in order to validate the results and assess if post-treatment expectations may result in a decreased use of relief medication and the associated cost savings.

5. Conclusions

In summary, the most prominent factors which could contribute significantly to the increased efficacy of acupuncture were, within a post-treatment horizon of the follow-up period, positive patients' expectations and low baseline levels of depression, fear of needles, and anticipation of the occurrence of migraines. The placebo effect of acupuncture in connection with the expectations of the patient tends to diminish. In a post-follow-up, the patient's positive perception of the TCM practitioner enhanced the post-follow-up efficacy of acupuncture. The preparation of the patient for treatment should include psychotherapy as a prerequisite for a re-calibration of expectations and good mental status. Nevertheless, future research should test whether interventions targeting those modifiable non-specific factors prior to and during acupuncture treatment can result in better patient outcomes and cost savings.

Authors

All research done by the authors

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Conflict of interest

none

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