



# The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain

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## Abstract

In a pooled analysis of four randomized controlled trials of acupuncture in patients with migraine, tension-type headache, chronic low back pain, and osteoarthritis of the knee we investigated the influence of expectations on clinical outcome. The 864 patients included in the analysis received either 12 sessions of acupuncture or minimal (i.e. sham) acupuncture (superficial needling of non-acupuncture points) over an 8 week period. Patients were asked at baseline whether they considered acupuncture to be an effective therapy in general and what they personally expected from the treatment. After three acupuncture sessions patients were asked how confident they were that they would benefit from the treatment strategy they were receiving. Patients were classified as responders if the respective main outcome measure improved by at least fifty percent. Both univariate and multivariate analyses adjusted for potential confounders (such as condition, intervention group, age, sex, duration of complaints, etc.) consistently showed a significant influence of attitudes and expectations on outcome. After completion of treatment, the odds ratio for response between patients considering acupuncture an effective or highly effective therapy and patients who were more sceptical was 1.67 (95% confidence interval 1.20–2.32). For personal expectations and confidence after the third session, odds ratios were 2.03 (1.26–3.26) and 2.35 (1.68–3.30), respectively. Results from the 6-month follow-up were similar. In conclusion, in our trials a significant association was shown between better improvement and higher outcome expectations.

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## 1. Introduction

Many clinicians believe that the expectations of patients can influence their health outcomes. Two systematic reviews have concluded that in spite of the limited number of rigorous clinical studies on the topic there is considerable evidence supporting this belief

(Crow et al., 1999; Mondloch et al., 2001). According to a common concept outcome and self-efficacy expectations are distinguished (Bandura, 1977). Outcome expectations refer to the consequences that follow an intervention while self-efficacy expectations are beliefs that one can successfully perform the actions required to achieve valued outcomes. Outcome expectations and subsequent neurobiological changes are considered to play a significant role in placebo analgesia (Benedetti, 2002; Finnis and Benedetti, 2005). Functional brain imaging studies have shown that expectation-related

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placebo analgesia may affect the affective and cognitive dimensions of the pain experience as well as the sensory-discriminatory dimension (Wager et al., 2004).

Within the framework of clinical trials the influence of expectations on outcomes could be of relevance both for within-group changes (from baseline to follow-up) and between-group differences (between the “true” treatment and placebo). For example, if a trial recruits a sample of patients with very positive attitudes towards the investigated interventions this could result in within-group changes which are larger than in a more representative sample. At the same time, high expectations might also be associated with high response rates in the placebo control group which makes it more difficult to detect additional “specific” effects over placebo (ceiling effect).

We have performed four randomized controlled trials comparing acupuncture, minimal acupuncture (superficial needling at non-acupuncture points) and a no treatment waiting list control in patients with migraine (Linde et al., 2005), tension-type headache (Melchart et al., 2005), chronic low back pain (Brinkhaus et al., 2006), and osteoarthritis of the knee (Witt et al., 2005). All trials found a large effect of both acupuncture and minimal acupuncture over waiting list, but only the osteoarthritis trial showed a significant effect of acupuncture over minimal acupuncture for the main outcome measure. In all four trials we also had asked patients about their attitudes regarding acupuncture in general and about their expectations regarding their individual outcome. The answers to these questions indicated that the participants had very positive attitudes and high outcome expectations. In the pooled post-hoc analysis of all four trials presented in this paper, we investigated whether patient expectations were associated with response to treatment. Our hypothesis was that patients with higher expectations would have been more likely to experience clinically relevant improvements than patients with lower expectations independently from allocation to acupuncture and minimal acupuncture.

## 2. Methods

### 2.1. Design, patients and interventions

The detailed methods and results on efficacy of the four trials have been published elsewhere (Linde et al., 2005; Melchart et al., 2005; Witt et al., 2005; Brinkhaus et al., 2006). 302 patients with migraine with or without aura, 270 patients with episodic or chronic tension-type headache, 298 patients with chronic low back pain, and 296 patients with osteoarthritis of the knee were randomized in a 2:1:1 ratio to either semi-standardized acupuncture treatment, standardized minimal acupuncture treatment (superficial needling of non-acupuncture points) or a no treatment waiting list control. Minimal acupuncture served as a sham control intervention. Patients were blinded for the comparison of acupuncture to minimal acupuncture. Both the acupuncture

and the minimal acupuncture intervention consisted of 12 treatment sessions of 30 min duration applied over 12 weeks. Acute pain could be treated in all groups with analgesics or nonsteroidal anti-inflammatory drugs (in the migraine trial also triptans) but such treatment had to be documented in a diary. Patients were informed with respect to acupuncture and minimal acupuncture in the study as follows: “In this study, different types of acupuncture will be compared. One type is similar to the acupuncture treatment used in China. The other type does not follow these principles, but has also been associated with positive outcomes in clinical studies”. The study protocol was approved by the relevant ethical review boards.

### 2.2. Outcome measurement

Main outcome measures were: in the migraine trial the number of days with moderate or severe headache in the 4 weeks after completion of treatment (weeks 9–12 after randomization); in the tension-type headache trial: the number of days with headache in the 4 weeks after completion of treatment (weeks 9–12 after randomization); in the low back pain trial: pain intensity measured on a 100 mm visual analogue scale after treatment (end of week 8); in the osteoarthritis trial: the WOMAC (Western Ontario and McMaster Universities Osteoarthritis) score after treatment (end of week 8). These outcomes were also calculated for exploratory analyses for the weeks 21–24 after randomization in the headache trials and at the end of month 6 and month 12 after randomization in the other two trials. In addition, patients in all trials completed a modified version of the pain questionnaire of the German Society for the Study of Pain (Nagel et al., 2002) which includes the German version of the Pain Disability Index (PDI; Dillmann et al., 1994) as well as a number of other validated scales.

In order to account for patient expectations and to relate this to the main outcomes, patients were asked the following two questions at baseline:

1. “How effective do you consider acupuncture in general?” Answer options were “very effective, effective, slightly effective, not effective, don’t know”.
2. “What do you personally expect from the acupuncture treatment you will receive?” Answer options were “cure, clear improvement, slight improvement, no improvement, don’t know”.

After the third treatment session patients were asked to answer four questions previously used in trials of acupuncture to test the credibility of the study interventions and, thus, the success of blinding (Vincent, 1990). One of these questions also relates to personal expectations: “How confident do you feel that this treatment can alleviate your complaint?” This question is answered on a 7-point Likert scale with the poles 0 = not certain at all and 6 = totally certain.

### 2.3. Analyses

Relevant data from the four trials were pooled in a SPSS file. Since the focus of our analyses was on patients receiving immediate treatment ( $n = 864$ ), the data from patients allocated to the waiting list group were deleted from the database

( $n = 304$ ). Sociodemographic variables, baseline values and expectations in the 4 trials were compared using analysis of variance and the  $\chi^2$  test. For further analyses the answers to the three questions related to expectations were dichotomized (patients responding with one of the two highest options versus remaining patients). The  $\kappa$  index was used to quantify the influence of chance in the dichotomized answers relating to expectations ( $\kappa < 0.4$  is considered poor agreement; 0.4–0.59 fair; 0.6–0.74 good;  $\geq 0.75$  excellent (Orwin, 1994)).

We calculated the proportions of patients with at least 50% improvement (response) for the main outcome measure in each trial both after treatment and at follow-up after 6 months compared to baseline values. As the trials had different main outcome measures, we also calculated responders for an outcome of major importance identical in all trials, the Pain Disability Index. The  $\chi^2$  test was used to investigate differences in responder rates between the 4 trials. To investigate the impact of expectations on outcomes we first calculated odds ratios and their respective 95% confidence intervals for the four responder outcomes for all three questions comparing patients with high expectation with the remaining patients (thus, we calculated 12 odds ratios). To take potential confounders into account, we then performed multivariate logistic regression analyses. The following variables were chosen: group allocation, condition (three dummy variables whether patients had migraine or not, tension-type headache or osteoarthritis), age, gender, education, duration since onset of complaints, degree of chronicity according to a staging system which is used widely in Germany (Gerbershagen, 1986), previous use of acupuncture, the question of expectation that was of interest in the specific analysis and an interaction term for expectation and group allocation. Due to multi-collinearity we included only one expectation question at a time. Both forward and backward selection using Wald test statistics were run to identify significant predictors of outcome; results were highly consistent with both selection methods. In the results section we present odds ratios and  $p$ -values from the logistic model established after variable selection.

### 3. Results

#### 3.1. Characteristics and expectations of patients

A total of 864 patients were included in the analyses: 226 with migraine (145 allocated to acupuncture and 81 allocated to minimal acupuncture), 195 with tension-type headache (132 and 63), 219 with chronic low back pain (146 and 73), and 224 with osteoarthritis of the knee (149 and 75). Sociodemographic characteristics and baseline values for pain outcomes, disability, depressive mood and quality of life differed to a considerable extent between the participants in the four trials (Table 1). Patients with headaches were younger, more often female, had lower body mass index, and higher education. Although attitudes towards acupuncture were very positive in all trials, there were significant differences between the trials (Table 2). Patients with osteoarthritis of the knee and chronic low back pain more often considered acupuncture a very effective therapy than did patients with headaches. In all four trials most patients expected a clear improvement from treatment. After three treatment sessions the majority of patients were highly confident that they would benefit from the treatment they received, however, there were significant differences between trials with osteoarthritis patients being the most optimistic. Patients receiving acupuncture or minimal acupuncture gave very similar answers ( $p = 0.94$ ). Assuming acupuncture to be a highly effective or effective therapy did not necessarily mean that patients reported a high expectation about their improvement. The agreement between the answers to the three questions regarding expectations over the agreement expected by chance was statistically highly significant ( $p < 0.001$ ) but modest ( $\kappa$  between 0.18 and 0.21).

Table 1  
Patient characteristics and baseline values in the four trials

	Migraine ( $n = 226$ )	TTH ( $n = 195$ )	Low back pain ( $n = 219$ )	Osteoarthritis ( $n = 224$ )
Age	42.6 (11.3)	42.6 (13.3)	58.8 (9.0)	64.1 (6.4)
Female	89%	72%	68%	69%
Body mass index	23.8 (4.0)	24.5 (4.0)	26.6 (4.4)	29.3 (4.8)
Secondary school completed	38%	40%	15%	12%
Duration of complaints (years)	20.3 (11.9)	14.7 (12.1)	14.3 (10.8)	9.4 (8.2)
Days with activities impaired <sup>a</sup>	27.1 (19.9)	41.0 (40.7)	93.1 (60.5)	108.5 (65.9)
Pain disability index (PDI)	33.8 (16.4)	21.6 (11.3)	29.8 (11.2)	27.9 (13.8)
Pain affective (SES) <sup>b</sup>	55.8 (8.9)	48.5 (7.6)	50.4 (8.3)	48.9 (9.1)
Pain sensoric (SES) <sup>b</sup>	54.7 (8.5)	47.2 (7.4)	49.5 (8.8)	52.9 (10.0)
Depressive symptoms (CES-D) <sup>b</sup>	49.6 (8.8)	52.0 (9.1)	53.0 (7.6)	51.2 (9.3)
SF-36 physical health sum scale	42.5 (7.4)	43.3 (7.1)	32.5 (8.2)	29.7 (7.6)
SF-36 mental health sum scale	47.4 (10.1)	45.1 (11.0)	48.3 (10.8)	51.6 (11.9)
SF-36 bodily pain scale <sup>b</sup>	36.1 (14.5)	44.8 (13.6)	34.3 (14.3)	32.6 (14.2)

Values are percentages or means (standard deviations). TTH, tension-type headache; PDI, pain disability index; SES, schmerzempfindungsskala (scale for measuring sensoric and affective aspects of pain); CES-D, centre of epidemiological studies depression scale and SF-36, short form 36 questionnaire for health-related quality of life.

<sup>a</sup> Within the last 6 months.

<sup>b</sup> Standard  $t$  scores.

Table 2  
Attitudes and expectations towards acupuncture at baseline and after three treatment sessions

	Migraine (%)	TTH (%)	Low back pain (%)	Osteoarthritis (%)	<i>p</i> -value <sup>b</sup>
<i>At baseline</i>					
I believe acupuncture to be					<0.001
Very effective	24	19	38	43	
Effective	54	58	35	28	
Slightly effective	<1	–	–	2	
Not effective	–	–	–	–	
Don't know	21	24	27	27	
Personal expectations					0.115
Cure	8	12	9	6	
Clear improvement	84	73	81	82	
Slight improvement	8	12	10	10	
No improvement	–	–	–	–	
Don't know	<1	2	<1	2	
<i>After session 3</i>					
Confidence <sup>a</sup>					0.001
6	29	27	41	46	
5	39	37	33	32	
4	24	23	17	14	
3	8	10	7	8	
<3	–	3	2	1	

<sup>a</sup> Confidence, How confident are you that this treatment can alleviate your complaint? Likert scale from 0 (not confident at all) to 6 (very confident).

<sup>b</sup>  $\chi^2$  test (belief and personal expectation) or Kruskal–Wallis test (confidence; four-group comparison).

### 3.2. Comparison of response rates

In the patients receiving the “true” acupuncture intervention, the proportion of patients reporting at least 50% improvement was very similar across the four conditions for the main outcome measure after treat-

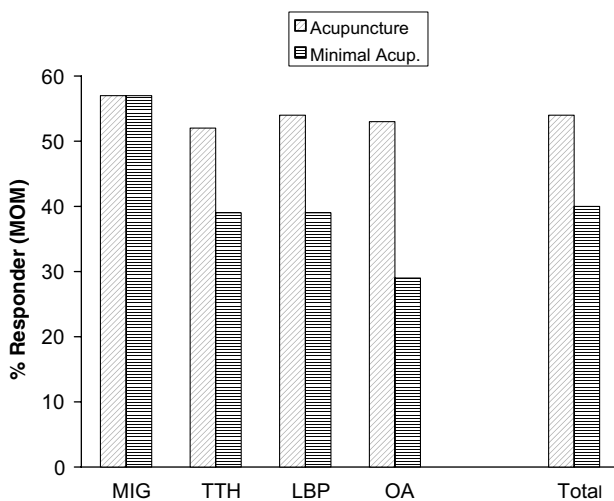


Fig. 1. Proportion of responders (patients reporting at least 50% improvement after treatment compared to baseline for the respective MOM, main outcome measure) in the four trials separately (MIG, migraine; TTH, tension-type headache; LBP, low back pain and OA, osteoarthritis of the knee) and if all trials are pooled (total). Differences between acupuncture and minimal acupuncture groups are statistically significant ( $p < 0.05$ ) for the low back pain trial, for the osteoarthritis trial and for the pooled analysis.

ment (see Fig. 1), at follow-up and for disability after treatment. A significant difference was found only for disability at follow-up. Instead, in patients receiving the minimal acupuncture intervention, differences across conditions were significant for three of four response measures (with migraine patients showing the highest and osteoarthritis patients the lowest response rates). In patients with osteoarthritis of the knee “true” acupuncture was statistically significantly superior to minimal acupuncture for all four outcome measures and in patients with low back pain for the dichotomized main outcome measure after treatment. There were no significant differences between the acupuncture and the minimal acupuncture group in the proportion of responders for the other outcome measures in the low back pain trial and in any outcome measure in the trials in migraine and tension-type headache. When findings were (pooled across conditions there were significantly more responders in the acupuncture groups compared to the minimal acupuncture groups after treatment (pooled odds ratio 1.75 (95%CI 1.28–2.31) for the dichotomized main outcome measure and 1.44 (95%CI 1.06–1.94) for disability but not at follow-up (odds ratios 1.14, 95%CI 0.85–1.54, and 1.13, 95%CI 0.83–1.54)). These findings were confirmed in the multivariate analyses.

### 3.3. Impact of expectations on response rates

Positive attitudes towards acupuncture, high personal expectations and confidence in benefit from treatment

Table 3  
Impact of expectation on outcome

Item (n with higher expectation/n with lower expectation)	Responder*	Univariate analysis		Multivariate analysis***	
		Odds ratio (95%CI)	p**	Odds ratio (95%CI)	p
<i>Response main outcome measure</i>					
Acupuncture at least effective/other (601/201)	52%/40%	1.67 (1.20; 2.30)	0.002	1.67 (1.20; 2.32)	0.002
Expectation at least clear improvem./other (718/87)	51%/33%	2.11 (1.32; 3.34)	0.001	2.03 (1.26; 3.26)	0.003
Confidence received therapy helps high/other (577/228)	54%/39%	1.80 (1.32; 2.46)	<0.001	2.35 (1.68; 3.30)	<0.001
<i>Response main outcome measure at follow-up</i>					
Acupuncture at least effective/other (594/194)	49%/38%	1.58 (1.13; 2.20)	0.008	1.54 (1.10; 2.15)	0.011
Expectation at least clear improvem./other (703/87)	48%/34%	1.76 (1.10; 2.80)	0.017	1.73 (1.09; 2.77)	0.021
Confidence received therapy helps high/other (566/226)	49%/40%	1.47 (1.07; 2.01)	0.018	1.56 (1.14; 2.15)	0.006
<i>Response pain disability index</i>					
Acupuncture at least effective/other (605/198)	44%/28%	2.04 (1.44; 2.89)	<0.001	2.02 (1.42; 2.97)	<0.001
Expectation at least clear improvem./other (719/87)	43%/18%	3.31 (1.88; 5.80)	<0.001	3.89 (2.19; 6.90)	<0.001
Confidence received therapy helps high/other (577/229)	44%/31%	1.79 (1.29; 2.74)	<0.001	2.21 (1.56; 3.13)	<0.001
<i>Response pain disability index at follow-up</i>					
Acupuncture at least effective/other (590/193)	48%/33%	1.84 (1.31; 2.59)	<0.001	1.71 (1.20; 2.43)	0.003
Expectation at least clear improvem./other (699/86)	46%/30%	1.97 (1.21; 3.20)	0.006	2.02 (1.23; 3.31)	0.005
Confidence received therapy helps high/other (560/226)	46%/39%	1.33 (0.97; 1.83)	0.081	2.21 (1.47; 3.32)	<0.001

\* % Responder among patients with higher expectations/% responder among patients with lower expectations.

\*\* Fisher's exact test.

\*\*\* Logistic regression (Wald forward selection) with adjustment for treatment group, condition, age, sex, education, previous acupuncture, chronicity staging, duration since onset of complaints, interaction term treatment group × expectation. Only one question related to expectation was included in the separate analyses.

were consistently associated with significantly better outcomes both after completion of treatment and at follow-up, both in the univariate and the multivariate analyses (see Table 3 and Fig. 2). For patients considering acupuncture as a highly effective or effective therapy compared with those being more skeptical, the adjusted

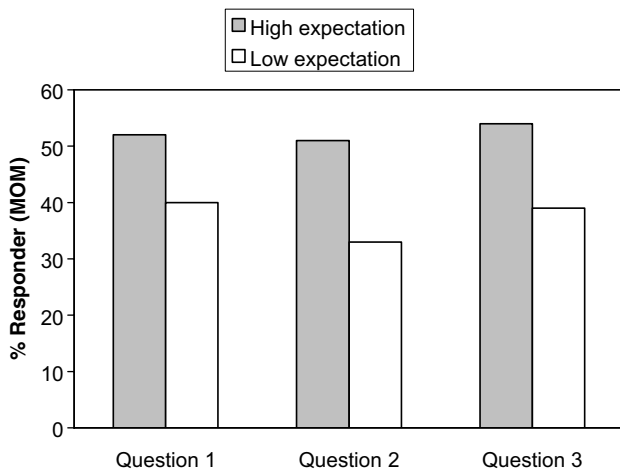


Fig. 2. Proportion of responders (patients reporting at least 50% improvement after treatment compared to baseline for the respective MOM, main outcome measure) in patients with high expectations compared to those with low expectations (pooled across conditions). Question 1 (at baseline): “How effective do you consider acupuncture in general?” Question 2 (at baseline): “What do you expect personally from the acupuncture treatment you will receive?” Question 3 (after session 3): “How confident do you feel that this treatment can alleviate your complaint?”

odds ratio for having at least 50% improvement in the main outcome measure was 1.67 (95% confidence interval 1.20–2.32). For personal expectations and confidence after the third session, the odds ratios were 2.03 (1.26–3.26) and 2.35 (1.68–3.30), respectively. The impact of expectations on outcome seemed slightly less pronounced in patients receiving minimal acupuncture than in patients receiving “true” acupuncture (see Fig. 3). This is confirmed by the multivariate analysis. The interaction term for expectations and treatment allocation became significant in four of 12 analyses.

### 3.4. Influence of other variables on outcome

In the multivariate analysis patients with osteoarthritis of the knee were less likely to be responders at follow-up than patients suffering from one of the other three conditions. Older age was also associated with lower response in four analyses. Gender, education, and previous use of acupuncture were not associated with response in any analysis.

## 4. Discussion

### 4.1. Major findings

In our four randomized trials patients with high expectations were more likely to report better outcomes than patients with lower expectations both after treatment and four months later. The size of expectation

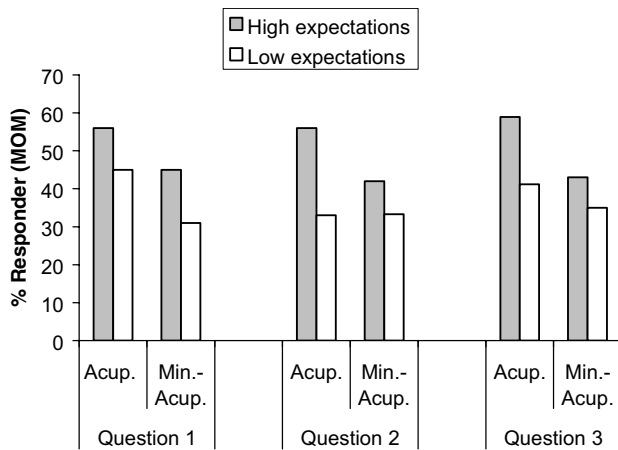


Fig. 3. Impact of expectations on response (patients reporting at least 50% improvement after treatment compared to baseline for the respective MOM, main outcome measure) in patients receiving “true” compared to minimal acupuncture. Question 1 (at baseline): “How effective do you consider acupuncture in general?” Question 2 (at baseline): “What do you expect personally from the acupuncture treatment you will receive?” Question 3 (after session 3): “How confident do you feel that this treatment can alleviate your complaint?”

effects is (with odds ratios around 2) clearly clinically relevant. This effect was observed both in patients receiving the “true” and the minimal acupuncture, but it seemed slightly less pronounced in the latter. Independently from expectation the proportion of responders in the pooled analysis was higher in patients receiving the “true” acupuncture than in those receiving minimal acupuncture after treatment but not at follow-up.

#### 4.2. Strengths and limitations

Compared to most available investigations on the influence of expectations on outcome, our analyses involve a much larger number of patients and cover a much longer observation period. The large sample size enabled us to control for potential confounders in multivariate analyses. Three different questions were used to measure attitudes and expectations. Two different outcomes were measured at two time points, and we performed both uni- and multivariate analyses. The findings were highly consistent.

However, a number of limitations have to be considered when interpreting our results. The primary objective of our trials was to investigate the effectiveness of acupuncture. While we included the questions on expectations because we had a general interest to investigate their impact this was not a pre-specified major aim of the studies and the methods to measure expectations were simplistic. Expectations can have a variety of aspects and can change over time (Stone et al., 2005). The answers to our three questions correlate significantly, but the low  $\kappa$  indices indicate that

they seem to address different aspects of expectations. In our multivariate analyses we only included one question per analysis as the simultaneous inclusion of all three questions resulted in less consistent results (for some outcomes all three questions had significant impact, for some two and for other only one).

The patients in the four trials differed considerably and the analyses of the pooled data must be interpreted with caution. In general, in the overwhelming majority of patients, attitudes towards acupuncture and outcome expectations were very positive. Therefore, our analyses lack sufficient power to investigate reliably their impact in the four trials considered separately.

We cannot rule out with certainty that patients with higher expectations did not really *have* less pain but only *reported* less pain than patients with lower expectations. The finding that the impact of expectation on outcome was less consistent among patients receiving minimal acupuncture could indicate some bias due to unblinding. However, this could also be a chance result. Patients were randomized to acupuncture or minimal acupuncture in a ratio of 2:1. As most patients had high expectations the number of patients with low expectations in the minimal acupuncture groups was relatively small resulting in wide confidence intervals.

#### 4.3. Interpretation

There is clear evidence from research on placebo analgesia showing that, in principle, expectations can modify pain perception in the brain. Several lines of research indicate that expectations associated with the application of placebos activate endogenous opioid systems, however, non-opioid pathways are also likely to play an important role (Levine et al., 1978; Amanzio and Benedetti, 1999). Studies using functional magnetic resonance imaging (fMRI) have shown decreased activity in pain-sensitive regions due to expectations induced by application of a placebo (Wager et al., 2004). The activation of limbic structures influences affective elements of pain perception (Mayberg et al., 2002; Petrovic et al., 2002). There is good evidence that the use of a placebo is, in patients suffering from Parkinson’s disease, associated with the release of considerable amounts of dopamine (de la Fuente-Fernández et al., 2001). Dopamine also likely plays a relevant role in placebo analgesia (de la Fuente-Fernández and Stoessl, 2004). In summary, expectations of clinical benefit seem in general to be a major mechanism of placebo effects.

Intense and frequent provider-patient interaction, touch, needling pain, and an “exotic” framework could make acupuncture a strong “ritual” which is associated with stronger expectation effects than other interventions (Kaptchuk et al., 2000, 2006; Kaptchuk, 2002). Few studies have investigated the impact of expectations in relation to acupuncture. Bausell et al. (2005) found

that the beliefs of subjects undergoing dental surgery as to whether they were receiving true or sham acupuncture significantly predicted pain levels after surgery. The actual treatment had little impact on pain levels. In a trial comparing acupuncture and massage for chronic low back pain, Kalauokalani et al. (2001) found that patients who were randomized to the treatment which they would prefer if given a free choice did better than those receiving the less desired treatment. In a study using positron emission tomography Pariente et al. (2005) found that real acupuncture had specific physiological effects compared to placebo acupuncture (using a non-penetrating telescope needle) but expectancy and belief modulated the activity in component areas of the reward system.

In our trials patients receiving acupuncture and minimal acupuncture reported clinically relevant and lasting benefit after treatment. In all four conditions the size of the effect of minimal acupuncture over waiting list control clearly exceeded those found in average in pain trials including both a placebo and a no treatment control condition (Hróbjartsson and Göttsche, 2001, 2004). The findings of our osteoarthritis trial and of our pooled analysis of all four trials suggest that “true” acupuncture has some additional “specific” effects over minimal acupuncture, however, the size of these effects was small and their duration limited. One potential explanation for the high response rates in the minimal acupuncture groups could be physiological effects of the minimal acupuncture intervention. While needles were inserted superficially at non-acupuncture points minimal acupuncture clearly cannot be considered an inert intervention (Irnich and Beyer, 2002). Another or additional explanation for the high response rates in both groups supported by our findings could be effects associated with expectations. In summary, the findings of our trials might indeed overestimate the total effect of acupuncture (as the expectations of our participants might have been over average) and, at the same time, underestimate point-specific effects (due to the strong effects in the minimal acupuncture group).

Further research on the impact of expectations on outcomes is definitively needed. The elucidation of mechanisms and clearly defined single aspects is predominantly the domain of strictly controlled experimental studies in the laboratory setting (Colloca and Benedetti, 2005). However, the measurement of variables related to expectations in long-term clinical multi-centre trials should become more widespread to investigate the clinical relevance of expectation effects and whether they might confound or modulate specific intervention effects (Finnis and Benedetti, 2005). The methods to measure expectations used in clinical trials so far are highly variable; similar to our trials patients are most often asked to answer one or a few simple questions addressing outcome expectations more or less

directly (Crow et al., 1999; Mondloch et al., 2001). Some researchers suggest that perceived treatment assignment (whether the patient believes that he received the true or the sham intervention) might be a good indicator of expectations (Stoessl and de la Fuente Fernandez, 2004; Benedetti, 2005). However, if patients make their guesses after clinical changes become apparent it is unclear whether the perceived treatment influenced the outcome or whether the perceived outcome influenced the guess (see for example, McRae et al., 2004). Compliance also might be associated with expectations or attitudes towards the treatment. It has been shown repeatedly that patients with good adherence tend to have better outcomes than patients with poor adherence even if they receive placebo (Simpson et al., 2006). A direct way to investigate the impact of expectations is in experiments according to the open hidden paradigm (Finnis and Benedetti, 2005). In such experiments patients receive an intervention either in an open or covert manner (for example, a specific drug is added to an infusion without knowledge of the patient). However, this approach is rarely possible in the evaluation of complex interventions.

## 5. Conclusion

The pooled analysis of our four randomized trials provides further evidence that expectations have a significant impact on outcomes in patients with chronic pain over a period of several months. Efforts are needed to develop reliable and valid, yet simple tools for measuring aspects of expectations in clinical trials. We think that qualitative studies are necessary to develop such tools. Still, we believe that already now researchers should include simple questions addressing expectations into their study protocols routinely.

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