



Review

Acupuncture, psyche and the placebo response

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ABSTRACT

With growing use of acupuncture treatment in various clinical conditions, the question has been posed whether the reported effects reflect specific mechanisms of acupuncture or whether they represent placebo responses, as they often are similar in effect size and resemble similarities to placebo analgesia and its mechanisms. We reviewed the available literature for different placebos (sham procedures) used to control the acupuncture effects, for moderators and potential biases in respective clinical trials, and for central and peripheral mechanisms involved that would allow differentiation of placebo effects from acupuncture and sham acupuncture effects. While the evidence is still limited, it seems that biological differences exist between a placebo response, e.g. in placebo analgesia, and analgesic response during acupuncture that does not occur with sham acupuncture. It seems advisable that clinical trials should include potential biomarkers of acupuncture, e.g. measures of the autonomic nervous system function to verify that acupuncture and sham acupuncture are different despite similar clinical effects.

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1. Efficacy of acupuncture — more than placebo?

Ever since acupuncture became a widely accepted treatment strategy in various clinical conditions, especially in pain disease, a

controversy has arisen as to whether acupuncture in comparison to the respective control conditions (see below, [Section 2](#)) is an effective treatment option or whether the accounted acupuncture effects reflect merely a placebo response ([Enck et al., 2008](#)).

[Madsen et al. \(2009\)](#) metaanalysed 13 pain trials with a total of 3025 patients with tension headache (1 study), migraine (1), osteoarthritis (3), low back pain (3), post-OP pain (2), colonoscopy (1), fibromyalgia (1), and scar pain (1). They summarized that a small but significant effect of acupuncture was noticeable that corresponds

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to a 4 mm (2 mm to 6 mm) change on a 100 mm visual analogue scale and thus may not have any clinical relevance. A similar effect size had been noted before by the same authors for clinical improvements in trials in pain patients in the respective placebo arm of placebo-controlled drug trials (Hróbjartsson and Gøtzsche, 2001, 2004). This, according to the authors, allows them to conclude that acupuncture may generate merely a placebo response.

The most comprehensive recent review by Moffet (2009) identified 229 PUBMED listed papers published in 2005 and 2006, of which only 38 met quality criteria including a control group (sham acupuncture). In 22 of these studies, no difference between acupuncture and sham acupuncture was found: in another 9 studies, acupuncture and sham acupuncture were equally ineffective in improving the clinical condition under investigation, in the other 13 studies, both procedures were equally effective (Table 1).

This metaanalysis has raised significant attention and controversy (e.g. Cassidy, 2009) and has elicited doubts not only on the validity of acupuncture itself but also on sham acupuncture procedures (see below).

2. Acupuncture trial control procedures

While most acupuncture trials are still conducted (and published!) without appropriate control conditions, the implementation of standard control procedures has without doubts improved the reputation of acupuncture trials over the last decade. It needs to be kept in mind, however, that all controlled trials are based on the assumption that the efficacy of a novel treatment is shown only with significant superiority of the treatment compared to the control (“additive model” according to Kirsch (2000)). Equal efficacy of control and placebo procedures in a strict statistical sense thus disapproved the clinical usefulness.

2.1. Waiting list and “treatment as usual” as controls

Waiting list (WL) and “treatment as usual” (TAU) are common control strategies in all non-medication trials where an inert “placebo” treatment is difficult to provide, such as in psychotherapy, physical rehabilitation, surgery, and “mechanical” interventions (TENS, magnetic stimulation, acupuncture). While some of these therapies have developed their own strategy (e.g. sham surgery), others have relied on WL and TAU for quite some time. Their limitations are that patient expectation to receive effective therapy are at conflict with being randomized to routine treatment (which most of them will have experienced in the past already) and to delays in therapy onset (which may increase the placebo response, but also drop-out rates). This may significantly affect recruitment and compliance in trials, and may lead to biased patient populations in respective studies.

Table 1

Outcome of 38 clinical acupuncture trials with different control strategies of sham acupuncture (from: Moffet, 2009).

Sham acupuncture controls	Differences in outcome	No differences in outcome	
		More efficacy than with sham	Both effective Both ineffective
Wrong acupuncture points			
Normal insertion and stimulation	3	2	3
Superficial insertion/minimal stimulation	0	2	0
Using non-points			
Normal insertion and stimulation	10	1	4
Superficial insertion/minimal stimulation	3	8	2
Total	16	13	9

According to a review by Lundeberg et al. (in press), of the 9 trials in migraine ($n = 3$), low back pain (3), osteoarthritis (3), one third used WL and/or TAU only to control for unspecific effects. In a survey by Schneider et al. (2007a), of 18 trials in various gastrointestinal disorders, mostly IBS 6 used sham acupuncture, 6 compared acupuncture to drug treatments, each 1 compared to TENS and to acupuncture at other acupuncture points, and 4 had no control groups implemented at all. In the metaanalysis by Moffet (2008, 2009), 22 of 36 studies used TAU and other non-acupuncture therapies, of which most (18) reported significant clinical efficacy without controlling for the placebo effect.

On the other hand, “no-treatment” control groups have been mandated by critiques of the current placebo discussion (Hróbjartsson and Gøtzsche, 2001, 2004) to account for spontaneous variation of symptoms in many clinical trials that may falsely be attributed to the placebo response. When they metaanalysed studies that did so (Krogsbøll et al., 2009), they found that about half of the placebo response can be attributed to spontaneous remission; this was also true for included pain trials. They also noted, that the number of studies that used no-treatment controls is low, they are often with benign clinical conditions (smoking cessation, insomnia), and include most often non-medicinal interventions such as psychotherapy and acupuncture.

Evidently, WL controls as well as TAU lack credibility in many clinical areas, and certainly do so where pain patients ask for therapy. According to recent metaanalyses (Saarto and Wiffen, 2007; Quilici et al., 2009) many drug studies in acute and chronic pain are therefore conducted with comparator drugs rather than with placebos for ethical reasons. Surprisingly, only a few acupuncture trials have been conducted comparing acupuncture to drug therapy, e.g. only 6 of the 18 studies reported by Schneider et al. (2007a).

2.2. Minimal acupuncture as control condition

A commonly used sham procedure in acupuncture trials is “minimal acupuncture” by inserting a needle either at or near a TCM needling point and providing low-grade stimulation, e.g. with a lower intensity electrical stimulation or only by inserting the needle. This seems a specifically valid ethical argument to perform acupuncture trials in acutely ill patients since patients are not withheld therapy but only the degree of therapy intensity. This procedure resembles similarities with medicinal studies where a low (and likely ineffective) dose is compared to higher dosage of the drug under investigation.

As is evident from the published trials (Moffet, 2009), minimal acupuncture is often as effective as true acupuncture. In the review by Lundeberg et al. (in press), the 6 studies that used this control condition yielded similar though somewhat lower response rates than acupuncture but overall substantial improvement of clinical conditions. The so far largest acupuncture trial, the German Acupuncture Trial for Chronic Low Back Pain (GERAC) (Haake et al., 2007) that included more than 1000 patients both acupuncture and sham acupuncture were equally effective and superior to conventional treatment alone.

This is frequently taken as a confirmation that acupuncture therapy is an effective clinical therapy option (Haake et al., 2007), but as Schneider et al. (2006) have pointed out in their IBS trial, it may as well be taken as evidence that the response is merely an unspecific placebo effect, as long as different mechanisms of action for the acupuncture and the sham acupuncture efficacy cannot be ruled out (Schneider et al., 2007b). Lundeberg et al. (in press) and the same group in other papers (Lundeberg et al., 2008; Lund et al., 2009) argue, that minimal acupuncture is “not a valid placebo control” due to the physiological effects that minimal acupuncture procedures are able to elicit (see below, Section 4.). However, as long as the correct conclusion is drawn from the study, i.e. that efficacy is only confirmed if the difference between both study arms is significant, using minimal acupuncture only requires higher efficacy of the verum procedure. It is a conservative statistical argument (against overestimating the

acupuncture efficacy) if the control conditions simulates as many features of the verum procedure as possible.

2.3. The “Streitberger” needle and other sham acupuncture needles

To overcome the need for an appropriate sham acupuncture procedure in respective trials, Streitberger and Kleinhenz (1998) and subsequently others have developed specific sham acupuncture needles by either blunting (Tough et al., 2009) or by blunting and shortening true placebo needle (Takakura and Yajima, 2007), or by the use of needles of similar appearance that do not penetrate the skin but retract telescopically into the needle handle, invisible for the patient (McManus et al., 2007). These devices have been validated for efficacy and specifically for blinding (White et al., 2003; Takakura and Yajima, 2008; Tough et al., 2009) and appear to work properly. In the study by White et al. (2003), the “Streitberger needle” was able to hide the assignment to the true and sham acupuncture group in acupuncture-naïve subjects (Fig. 1).

These types of needles can be used in a similar fashion than the previously discussed sham acupuncture procedures, i.e. they can be either applied to acupuncture points or to skin areas adjacent to acupuncture points to minimize the risk of “minimal acupuncture” effects, as discussed. Applied in clinical trials, these placebo needles showed similar efficacy to true placebo in some conditions such as IBS (Schneider et al., 2006), but inferiority in others such as in postoperative nausea (Streitberger et al., 2004). Consequently, they raise the same concern: whether the observed improvements in clinical symptoms in the sham group is due to inappropriate control conditions allowing minimal acupuncture effects to occur under control conditions (Moffet, 2009; Lund et al., 2009; Lundeberg et al., *in press*). This question can only be resolved with mechanistic studies using peripheral and central recording techniques (see below).

2.4. Other control strategies for acupuncture trials

Besides technically modified needles for sham acupuncture, other techniques have been used to control for the specificity of the acupuncture treatment effects. Among them is sham electroacupuncture where acupuncture needles are inserted at either acupuncture points and adjacent and connected to an electrical stimulator, but no electrical stimuli are applied. This procedure needs specifically acupuncture-naïve patients (current knowledge on what to expect from acupuncture may be widespread) and additional patient information on what to expect to cover the placebo condition. However, with informed consent to be provided to all patients, unblinding of such a procedure is highly likely, and blinding procedures (see below) may be difficult to implement (Boutron et al., 2006; Machado et al., 2008).

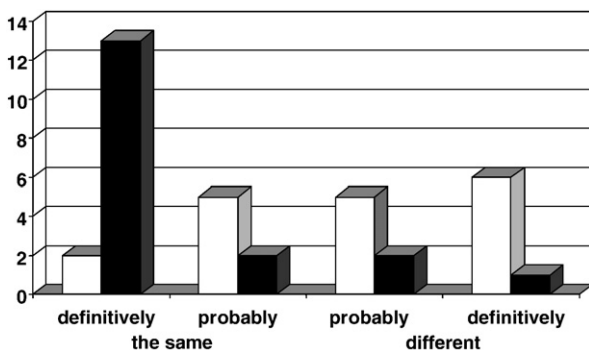


Fig. 1. Estimation of acupuncture-naïve patients whether they had received acupuncture and sham acupuncture at two occasions in a randomized sequence. Thirty-six patients (18 females) were stimulated by female and male practitioners in a balanced fashion. Significantly more patients believed that they had received true acupuncture at both occasions when the acupuncturist was female (black bars) (from: White et al., 2003).

3. How valid are sham acupuncture procedures?

Validity of control conditions not only in acupuncture trials depends to a great degree on a number of design factors that contribute to the placebo effect; among them are the degree of blinding, patient selection, and the therapist/physician's behavior applying the acupuncture procedure.

3.1. Blinding strategies

In a systematic review of 126 trials with different treatment options for low back pain, Machado et al. (2008) investigated appropriate and inappropriate blinding procedures, among them 10 acupuncture trials using different sham control strategies.

Only 4 of the studies assessed by Machado et al. (2008) assessed indistinguishability of the sham from the true acupuncture procedure, and only two used acupuncture-naïve subjects, making it likely in the others that the assumed “inertness” and blindness of the sham procedure may have been unmasked. The review by Madsen et al. (2009) noted that in their 13 trials metaanalysed none had blinded the acupuncturist. These problems are, however not specific to acupuncture trials, as with the other non-medicinal treatment options for low back pain (back school, behavioral treatment, electrotherapy, exercise, heat wrap therapy, insoles, magnet therapy, massage, neuroreflex therapy, spinal manipulative therapy, and traction) similar incomplete blinding problems were noted, while drug trials usually comply with this condition.

3.2. Patient/subject selection

Using non-naïve subjects in acupuncture trials is another issue that may account for placebo effects in most therapies, both with drug treatment as well as with complementary therapies (see Table 1). While in drug treatment it may account for high conditioned responses (based on Pavlovian conditioning of drug effects with previous trials (in fact, most double-blind placebo-controlled drug trials never assessed whether patients enrolled had participated in previous drug trials for the same condition)), in complementary and alternative medicine (CAM) studies it may account for a high self-selection of patients that prefer CAM therapies over drug therapy and are highly motivated to undergo such treatment. Overall however, placebo response rates in 31 CAM studies, e.g. in irritable bowel syndrome (Dorn et al., 2007) are similar than in drug trials in the same patient group (Enck and Klosterhalfen, 2005; Patel et al., 2005; Pitz et al., 2005). One option to avoid such a bias would be to assess the expectancies of patients prior to treatment and randomization. This may allow to predict the size of the placebo response in future trials (Halpert et al., 2010).

3.3. Moderators of response: physician's behaviour

While it is widely accepted that the placebo response not only in acupuncture trials is driven by patient expectations and beliefs and previous experience with medical interventions, the role of the physician performing the treatment is acknowledged but less well investigated.

A good example from the acupuncture literature is the study by White et al. (2003) validating a sham acupuncture needle. In this study, patients were asked whether they had received acupuncture or sham acupuncture, to test for the complete blinding of the procedure. While most patients were unable to judge the group's assignment, their belief was modulated by the gender of the experimenter: if this was a female physician, patients significantly more often believed that they had received true acupuncture.

A systematic investigation of the role of physician variables in the efficacy of (sham) acupuncture treatment is documented in the

study by Kaptchuk et al. (2008). Acupuncture-naïve patients with irritable bowel syndrome (IBS) were randomized to either WL control, or to sham acupuncture alone, or to “augmented” sham acupuncture; in the latter, the sham acupuncture procedure was accompanied by a number of different physician behaviors related to both content and style of patient–physician interaction: *content* included questions concerning symptoms, how irritable bowel syndrome related to relationships and lifestyle, possible non-gastrointestinal symptoms, and how the patient understood the “cause” and “meaning” of his or her condition. *Behaviors* included a warm, friendly manner; active listening thoughtful silence while feeling the pulse or pondering the treatment plan; and communication of confidence and positive expectation. Half of the patients in each group were offered true acupuncture treatment after 6 months.

After three and after six weeks of treatment, sham acupuncture was significantly superior to WL control, but patients in the “augmented” sham treatment (group 3) were significantly more improved on all outcome measures (global improvement, adequate relief, symptom severity, quality of life) compared to “pure” sham acupuncture (Fig. 2).

The authors conclude that results indicate that such factors as warmth, empathy, duration of interaction, and the communication of positive expectation might indeed significantly affect clinical outcome. In another paper from the same group (Kaptchuk et al., 2006), sham acupuncture was significantly more effective than a placebo pill treatment for somatosensory pain underlining the importance of placebo responses in acupuncture treatment.

4. Are acupuncture effects specific and distinguishable from sham procedures?

As long as acupuncture and sham acupuncture treatments produce similar clinical improvements, the results of respective trials can only be taken as evidence against the efficacy of acupuncture. Only when it can be shown that acupuncture and sham acupuncture effects are mediated differently, this can be taken as evidence that acupuncture effects are different from placebo effects, although both may still be equally effective.

4.1. Central effects of acupuncture versus sham acupuncture

A few studies so far have investigated central processing of acupuncture and sham acupuncture procedures. Acupuncture but not sham acupuncture was found to induce both cerebellar as well as limbic cortex activation indicating both motor as well as affective component modulation of the pain matrix. Acupuncture resp. electro-acupuncture at non-acupuncture points and tactile stimulation alone served as controls in early fMRI studies (Wu et al., 2002; Yoo et al., 2004). Verum acupuncture in contrast to non-penetrating placebo

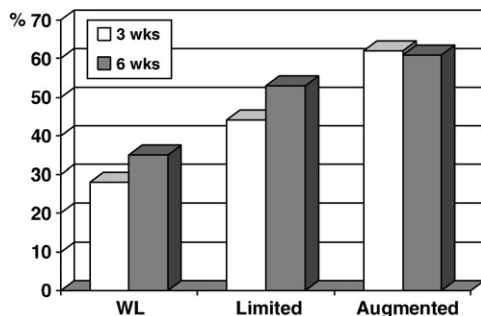


Fig. 2. Percentage of IBS patients experiencing adequate relief of symptoms during sham acupuncture treatment compared to waiting list (WL) controls. Patients in the sham acupuncture group received either limited attention of the acupuncturist or augmented attention during which the behavior of the acupuncturist was modulated both by content and by style of patient–physician interaction (from Kaptchuk et al., 2008).

needles activated cortical centers involved in affective pain modulation also in more recent studies (Chae et al., 2009). It was, however, noted that cortical activation following acupuncture shows substantial within as well as between-subject variations across different sessions (Kong et al., 2006).

Differences between true and sham acupuncture were also found for the same regions by Napadow et al. (2009a); these authors also noted greater activation of sensorimotor areas (S1,S2, insula) by their sham procedure (superficial manipulation at acupuncture points) than by true acupuncture. In another study of the same group, Napadow et al. (2009b) noted variances in time of central activation between verum and sham acupuncture that they attributed to stronger peripheral actions of true acupuncture (see Section 4.2).

In a recent ^{11}C -carfentanil PET study with fibromyalgia patients (Harris et al., 2009), acupuncture therapy but not sham acupuncture (at non-acupuncture points) elicited significant activation of mu-opioid receptor binding capacity in typical areas of the “pain matrix”, the cingulate, the caudate, the thalamus and the amygdala both short-term (after one session) as well as long-term (after 4 weeks) while with sham acupuncture, small deactivations of this matrix was noted, an effect that has been seen also with placebo analgesia (Zubieta et al., 2005) (see Section 4.2).

4.2. Peripheral (autonomic) effects of acupuncture versus sham acupuncture

Very few recent studies have investigated the peripheral responses between true and sham acupuncture. In the IBS study by Schneider et al. (2006), peripheral responses to true and sham acupuncture were reported in another paper by the same group (Schneider et al., 2007b). Here they described significant differences between true acupuncture compared to controls (sham acupuncture with the “Streitberger” needle at non-acupuncture points) in tonic (diurnal profile of saliva cortisol) and phasic autonomic responses (heart rate variability following a cardiac challenge) (Fig. 3).

While with acupuncture, both measures were significantly correlated, this was not the case with sham acupuncture indicating a sustained and consistent parasympathetic activation after acupuncture treatment while the response in the control groups resembles more the effects of a placebo response. As the authors point out, placebo and verum effects not only with acupuncture treatment often look similar with clinical efficacy endpoints (e.g. in depression treatment when the

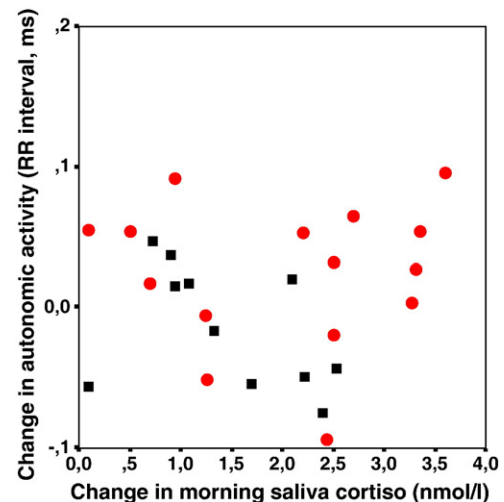


Fig. 3. Maximal change in saliva cortisol (nmol/l) (7:00 a.m. value pre- and post-therapy) plotted against the change in RR interval (ms, supine minus orthostasis) prior and post-therapy. As is evident, this correlation was negative indicating parasympathetic stimulation with acupuncture (squares) that yielded statistical significance while in sham acupuncture (dots) no such association can be found (from: Schneider et al., 2007b).

Hamilton Anxiety Depression Scale is used, see Leuchter et al., 2002), and require the inclusion of moderators of efficacy for better distinction of true treatment and placebo effects.

5. Are acupuncture analgesia and placebo analgesia the same?

A valid example is the modulation of experimental or clinical pain with acupuncture (and to some degree also with sham acupuncture procedures) and with deliberate placebo application (placebo analgesia) (Levine et al., 1981). While the latter has a long tradition in clinical medicine, its mechanisms have only recently been investigated. In the above cited study (Zubieta et al., 2005) and in other studies it was shown that placebo analgesia is associated with sustained striatal dopamine release (Scott et al., 2007), and that placebo-induced hyperalgesia is inversely related to the release of opioids (Scott et al., 2008) indicating a coupling of the pain matrix and the reward system. The striatal reward system has also been shown to be activated when acupuncture (or sham acupuncture) is expected to elicit relief in pain patients (Pariente et al., 2005) irrespective of whether or not acupuncture and sham acupuncture procedures elicited analgesic responses (which they did not).

In an attempt to explore the associations between both analgesic mechanisms, Kong et al. (2009) investigated acupuncture and sham acupuncture (Streitberger needle) with and without expectancy manipulation in healthy subjects in a cross-over design and found that both acupuncture and sham acupuncture – when coupled with high expectation – produce analgesia of similar magnitude, but the verum acupuncture elicits higher deactivation of the pain matrix than did sham acupuncture and expectancy analgesia alone. This also underlines different central mechanisms of analgesia between expectancy and acupuncture.

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