Trials of acupuncture for drug dependence: a recommendation for hypotheses based on the literature

Adrian White

ABSTRACT

Objectives: After initial promising research into acupuncture for withdrawal from drugs of dependence, two large negative trials were published in 2002 and the use of acupuncture in US rehabilitation facilities fell. However, subsequently it has been maintained, despite a lack of support from systematic reviews. This suggests a mismatch between research and clinical observation, which could be due to the acupuncture technique used, choice of controls or outcome measures. This study aims to explore the mismatch.

Methods: An exploratory review of all 48 clinical trials on alcohol, cocaine, nicotine or opioid dependence included in current reviews.

Results: Studies with sham controls (that could be active) were less likely to be positive (33%) than those with non-acupuncture controls (75%). Positive results were more likely when measuring craving (56%) or withdrawal symptoms (58%) than when measuring abstinence (31%) or attrition (31%). Three treatment variables appeared to be associated with positive results: (1) body acupuncture, used in 13 studies, was associated with positive outcomes for craving and withdrawal symptoms but not for abstinence or attrition (31%); (2) electroacupuncture, used in seven studies, was associated with positive results with all four outcomes; and (3) bilateral needling in 20 studies was associated with effects on abstinence, craving and withdrawal symptoms.

Conclusions: The current evidence suggests that acupuncture may have some effects on drug dependence that have been missed because of choice of outcome in many previous studies, and future studies should use outcomes suggested by clinical experience. Body points and electroacupuncture, used in the original clinical observation, justify further research.

BACKGROUND

The year 2002 marks a watershed for both research into and use of acupuncture for drug dependence.

Early trials of acupuncture for dependence had produced some astonishing results, such as 50% abstinence in opioid users1, 2 and a halving of drinking episodes and readmissions among severe alcohol recidivists.3 While providing some support for acupuncture, these results pointed to the need for well-designed randomised controlled trials (RCTs). In 2002, two large rigorous trials were reported with disappointing results. In a four-arm RCT of 503 alcohol-dependent participants, neither true nor sham acupuncture made any difference to attrition from the treatment programme or abstinence from alcohol.4 A study of 620 participants using cocaine found no differences between acupuncture, sham acupuncture or relaxation for either retention on the treatment programme or abstinence.5

The response of US drug dependence rehabilitation facilities to these negative studies on acupuncture was rapid, as shown in figure 1. The use of acupuncture rose before 2002, reaching over 700, but then fell sharply over the following 3 years. However, the use of acupuncture has held steady since, with recent figures of 593 in 2010 and 599 in 2011. Acupuncture continued despite lack of support from systematic reviews, which summarised the evidence as ‘equivocal’ for alcohol,6 ‘inconclusive’ for auricular acupuncture for cocaine,7 ‘inconclusive’ for acupuncture for opioids8 and ‘no consistent bias-free evidence’ for smoking cessation.9

The fact that acupuncture is still widely used despite unsupportive evidence...
suggests a mismatch between practice and research. For example, trials may not use the optimal acupuncture technique (electroacupuncture (EA) and the use of body points might have useful effects\(^{10}\)) or trials may not be measuring outcomes that capture the true benefits of acupuncture. Cowan discussed the dissonance between patients’ reported experiences and the design of clinical trials and recommended qualitative studies on participants’ experiences of acupuncture.\(^{11}\)

In the hope of suggesting possible future directions for acupuncture research, this paper aims to explore quantitatively this mismatch between research and practice of acupuncture for drug dependence by examining the outcomes of published studies when combined in different ways.

**METHODS**

A review of RCTs of acupuncture for dependence on alcohol, cocaine, nicotine and opioids was conducted using a conservative (exploratory) analysis. Because of the heterogeneity of the studies, its aim was to explore hypotheses rather than to test them, generating impressions rather than conclusions.

All RCTs included in the most recent available systematic reviews of alcohol,\(^{6}\) cocaine,\(^{7}\) nicotine\(^{9}\) and opioids\(^{8}\) were considered. Information was extracted on participants, acupuncture treatment variables, control variables and outcome variables used (abstinence, attrition, craving and withdrawal symptoms). Data were extracted from the systematic review and from the full report when available. ‘Headline’ results, meaning the main outcomes in their simplest form, were extracted from each study for between-group comparisons. Reported differences between groups were only considered significant at the level of \(p<0.05\), and comparisons with different control groups (e.g., sham control or relaxation control) were not treated separately. Resources did not allow formal assessment of trial quality.

Considerable amounts of treatment data are missing from the reports, particularly whether or not treatment was bilateral, leading to uncertainty on the total number of needles used. By default, unilateral was assumed and means were calculated for ranges.

The analysis consisted of a simple ‘vote count’. This was facilitated by using the Custom Sort facility in Microsoft Excel, marking the variables with colour coding. Studies were grouped for each drug separately, then for each treatment variable; each study was counted as positive if any of the four outcomes (abstinence, attrition, craving and withdrawal symptoms) was positive. Finally, studies were grouped by the separate outcomes.

**RESULTS**

A total of 48 studies were included out of the 50 in the four reviews, as set out in table 1. The full dataset is available as online supplementary table 1a, with references to original studies. Data can be copied in order to add other data—for example, more information on variables such as frequency of electrical stimulation or other variables such as country of origin or whether the participant had already stopped using the drug when enrolled into the study—and to conduct other analyses.

The excluded studies\(^{12,13}\) compared different types of acupuncture and were uninterpretable for our purposes. The points described as ‘Han acupoints’ in one study were undefined.\(^{14}\) One study had a result which was inconsistent and was therefore excluded:
### Table 1  Essential characteristics of randomised controlled trials of acupuncture for dependence from four reviews grouped by drug, in date order

<table>
<thead>
<tr>
<th>1st author</th>
<th>Date</th>
<th>N</th>
<th>Points*</th>
<th>EA</th>
<th>Abstinence†</th>
<th>Attrition</th>
<th>Craving</th>
<th>Withdrawal symptoms</th>
</tr>
</thead>
</table>
#### Cocaine
- **Lipton** 1994 192 Auricular N Y N N
- **Avants** 1995 40 Auricular* N N N Y
- **Richard** 1999 236 Auricular N N N N
- **Otto** 1998 36 Auricular N N
- **Avants** 2000 82 Auricular N Y N
- **Margolin** 2002 620 Auricular N N N
#### Alcohol
- **Bullock** 1987 54 Auricular* N Y Y Y
- **Worner** 1992 56 Body* N N N
- **Toteva** 1996 118 Body Y Y Y Y Y
- **Rampes** 1997 59 Auricular Y N
- **Sapir-Weise** 1999 72 Auricular N N N N
- **Bullock** 2002 503 Auricular N N N N
- **Karst** 2002 34 Auricular* N N N
- **Trumper** 2003 48 Auricular N N N
- **Kim** 2005 22 Body N
- **Jin** 2006 35 Y N N
- **Kunz** 2007 109 Auricular N N N
#### Opioids
- **Washburn** 1993 100 Auricular N N Y
- **Wells** 1995 60 Auricular N N N N N
- **Zhang** 2000 181 Body Y Y
- **Montazeri** 2002 40 Body N Y
- **Wu** 2003 120 Body N Y Y
- **Wen** 2005 220 Body N
- **Margolin‡** 2005 40 Auricular N N N
- **Zeng** 2005 70 Body N
- **Mu** 2005 120 Body Y
- **Bearn** 2009 83 Auricular N N N
#### Nicotine
- **Gilbey** 1977 92 Auricular N N
- **Lacroix** 1977 117 Face N Y
- **Parker** 1977 41 Auricular N‡ N
- **Vibes‡** 1977 200 Various N N
- **Laguerre** 1980 154 Face N N
- **Lamontagne** 1980 75 Auricular N N
- **Martin** 1981 260 Auricular N‡ N
- **Steiner** 1982 32 Body* N N
- **Cottraux** 1983 558 Face N Y Y
- **Labadie** 1983 130 Body* N N N
- **Gills‡** 1984 81 Auricular N N
- **Circo** 1985 90 Auricular N Y
- **Clavel** 1985 89 Face N N
- **Vandevenne** 1985 200 Body/face N N
- **Leung** 1991 95 Auricular N Y
- **Clavel** 1992 996 Face N N
- **He** 1997 46 Auricular* N Y Y
- **Waite** 1998 78 Auricular Y Y
- **White** 1998 76 Auricular Y N N
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*Continued*
measurement of withdrawal symptoms unadjusted was significant but became non-significant when adjusted for prespecified baseline confounding variables. The study was negative for its other outcome (attrition). The study by Bullock et al with four arms was entered twice for the comparison of manual and EA interventions.

About half of the studies (23/48) had at least one positive result. There was little difference between the success rates of studies with a sample size over 100 (11/21, 52%) and smaller studies (12/27, 44%).

Participants
Wen’s original observations on acupuncture were made on smokers of street opium in China in the 1970s. Since then, acupuncture has been applied to users of other classes of psychoactive drug, particularly cocaine, alcohol and tobacco. While stimulation of the so-called reward centre is common to all, each clearly also activates other brain mechanisms responsible for their various effects and side effects.

The proportions of positive findings were (in order): opioids (7/9), cocaine (4/7), alcohol (5/11) and nicotine (7/21).

Acupuncture intervention
Choice of points
Wen originally discovered the effect of acupuncture using ‘Lung’ auricular points and four body points—two pairs of points (LI4 with SI3 and PC4 with TE9) in the right arm only. The body points were not used in later studies, and Smith et al made no mention of body points when they introduced acupuncture to the Lincoln Hospital in the Bronx. Auricular points, particularly the National Acupuncture Detoxification Association (NADA) protocol, are now generally used in the West. The ready accessibility of the ear and simplicity of needle insertion are important factors in the attractiveness of acupuncture to users and therapists. However, body points seem to be more commonly used for treating dependence in China. For example, Han’s series of laboratory and clinical trials used LI4 with PC8 on one hand and PC6 with TE5 on the other arm.

Two studies were excluded from this analysis (no information; all locations used 21), and one was entered twice. Eight of 13 studies (62%) using predominantly body points were positive, 2/5 studies (40%) using face points were positive and 12/29 studies (41%) using auricular points were positive. The difference between body and auricular acupuncture is particularly marked when measuring craving and withdrawal symptoms (body points, 4/4, 7/7 positive; auricular points, 4/11, 0/5 for craving and withdrawal, respectively). The body point studies tended to use more needles and were less likely to use sham controls, but used fewer sessions on average (mean 13 vs 21).

Number of needles
Little empirical information exists on the minimum number of needles necessary to evoke an acupuncture effect. In the present review, 9/26 studies (35%) using <6 needles were positive, as were 14/21 studies (67%) using ≥6 needles. There are no gross differences between the two sets of studies in other treatment variables or in the proportion of studies that measured craving and withdrawal.

Bilateral needling
Use of bilateral needling was not associated with any increased effect overall: 3/5 with unilateral needling were positive as were 11/20 with bilateral needling (and 4/4 with probable bilateral needling), but a differential effect on outcomes was seen (discussed below).

Stimulation
Wen originally discovered the effect of acupuncture on withdrawal symptoms using EA but discontinued it, presumably because it was inconvenient. Lincoln Hospital discontinued EA because ‘manual acupuncture resulted in more consistent clinical outcomes’, anecdotally. In the NADA protocol, needles are not stimulated but are left in situ for about half an hour. Electrical stimulation is more common in China: Han has continued to use electrical stimulation in his studies. Rubber electrodes (transcutaneous electrical acupuncture stimulation, TEAS) are preferred to needles for comfort and simplicity since treatment is repeated frequently. The optimum effect has usually been with 2/100 Hz ‘dense-dispersal’ mode which releases both β-endorphin and dynorphin.

<table>
<thead>
<tr>
<th>1st author</th>
<th>Date</th>
<th>N</th>
<th>Points*</th>
<th>EA</th>
<th>Abstinence†</th>
<th>Attrition</th>
<th>Craving</th>
<th>Withdrawal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bier</td>
<td>2002</td>
<td>141</td>
<td>Auricular*</td>
<td>N</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han</td>
<td>2006</td>
<td>42</td>
<td>Body*</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu</td>
<td>2007</td>
<td>131</td>
<td>Auricular</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Indicates other locations also used.
†Indicates study not used in analysis (see text for explanation)
Yellow shading indicates use of EA, blue shading body points and green shading both EA and body points.
EA electroacupuncture; N, outcome used, not positive result; Y, outcome used, positive result.

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Seven of the 48 studies used EA and six of these (86%) were positive, which is about double the 41% rate of those without EA (17/41). However, five of the six positive EA studies used craving and withdrawal symptoms as an outcome—which we shall see below are more likely to be associated with positive results than abstinence or attrition.

Treatment schedule
Clinical impressions suggested that the effect of acupuncture on withdrawal was short-lived so it had to be repeated up to several times a day. An alternative method of continuing the stimulation is to insert an indwelling needle into the ear which can be stimulated by the patient, but was only used for nicotine dependence.

There is weak evidence from these studies that the schedule is important: 14/25 studies (56%) offering daily acupuncture sessions were positive, as were 5/14 (36%) that did not use daily sessions and 4/9 (44%) that used indwelling needles. These differences are not explained by other factors.

Approximately half (8/17) of the studies with <10 sessions were positive, which is a similar proportion to the 15/31 with >10 sessions

Control intervention
The choice of control must be driven by the known mechanism of action, or at least plausible theory. Specificity of points was widely believed historically, but has little neurophysiological basis and has been challenged in a review. There may be no such thing as ‘wrong’ points for the control group, just less active points. In particular, the concept of somatotopic representation in auricular acupuncture has been questioned. Non-penetrating sham devices have been produced, but any device that looks and feels like acupuncture also stimulates the nervous system.

One explanation for the negative results of sham controlled trials of auricular acupuncture, including the two high profile studies, may therefore be that they were comparing two active treatments. Some of the evidence here supports this. Twelve of the 16 trials (75%) comparing acupuncture with non-acupuncture controls were positive compared with 11/32 (34%) of the group comparing acupuncture with sham needle acupuncture. This difference is not explained by the proportion using the more promising outcomes (craving and withdrawal symptoms), but may of course be partly due to bias from unblinding. Against this, only two of the six studies using inactive sham controls were positive, although this could be related to their smaller sample sizes (mean N=33) than the active sham group (mean N=172), increasing the risk of false negative results.

Outcome assessment
People withdrawing from drugs or alcohol seem to appreciate acupuncture for bringing calmness and cooperativeness. Wen described the effect of acupuncture on patients during withdrawal as ‘immediate relief ... they felt good, were alert and relaxed’. In an extensive review, Brumbaugh stated that ‘patients seem more alert, relaxed, and report the ability to think clearly, and became more cooperative and more likely to participate in detoxification and rehabilitation programmes’. Cowan reported that ‘calmness and psychological and physical vitality are experienced with people reporting vastly improved sleep’. Stuyt and Mooker reported that acupuncture appeared to have ‘a significant calming effect’, as well as reducing anger and improving self-reported sleep.

Despite these observations, three-quarters of these studies measured abstinence from drugs, which is important but possibly inappropriate.

One early study showed an effect on retention in treatment programmes. Retention might be expected to be increased by the kind of effects that are described with acupuncture, although also influenced by other factors.

Two other outcomes have been measured in several studies: craving and withdrawal symptoms. Anxiety and depression, though not specifically features of withdrawal and recovery, have been measured but only rarely and are not considered further here. Table 2 summarises the data on the four outcomes. Positive results were rather more likely when measuring craving (9/16, 56% positive) or withdrawal symptoms (7/12, 58% positive) than when measuring abstinence (11/36, 31% positive) or attrition (5/16, 31% positive). Two treatment variables appeared to be associated with positive results: body acupuncture, used in 13 studies, was associated with positive outcomes for craving and withdrawal symptoms but not for abstinence or attrition; and EA, used in seven studies, was associated with positive results with all four outcomes. Bilateral needling also appeared to be associated with effects on abstinence, craving and withdrawal symptoms in 20 studies.

Timing of outcome
Because the effect of acupuncture is of limited duration, assessment should be made within a short time period, which Han suggests could be about 1 week. The outcome was assessed within a week of the last treatment in the majority of these studies.

DISCUSSION
Half of the clinical trials of acupuncture for dependence reviewed here had at least one positive result, supporting the concept that acupuncture has some beneficial effect in drug dependence, but the evidence is inconsistent because of the large number of variables in treatment and outcomes. RCTs using sham acupuncture controls are less likely to be positive than those using non-acupuncture controls, which could be due to active controls or bias. RCTs appear more...
likely to find positive effects on craving and withdrawal symptoms than on abstinence and attrition, suggesting these are better targets for investigation. Use of body acupuncture points rather than auricular points alone, use of EA and use of bilateral needling are also associated with positive results. These data need careful interpretation because of study limitations. Several groups of studies are small. The rigour of some of the primary studies is doubtful and many have some risk of bias. Presumably this bias will be mainly towards false-positive findings, but small studies are at risk of type II error which would underestimate the positive results using the ‘vote count’ procedure. Another limitation is that studies could have other differences that have not been considered here such as setting, drug status of participants at enrolment or frequency of EA.

Our current understanding of the mechanisms of acupuncture suggests that it could have a relevant role in the neurophysiology of dependence. Withdrawal symptoms and craving are recognised as complex and multidimensional but, according to the psychobiological model, craving is a function of the activity of the nucleus accumbens. Drugs of dependence stimulate dopamine release, and the response shows tolerance with habituation. Withdrawal of the drug leads to low levels of dopamine, inducing withdrawal symptoms and craving. There is support for the hypothesis that the opioid release stimulated by acupuncture helps restore the release of dopamine, and Han and colleagues even suggest different mechanisms of 2 Hz and 100 Hz stimulation in reducing craving. So acupuncture of different types may potentially have different roles to play at different stages of withdrawal and recovery. EA seems to have effects that accumulate when treatment is repeated and that then last for at least a week.

This exploration of the literature has implications for research. Trials need to compare the NADA protocol with truly inactive controls. More research is justified on the effects of body points, as already suggested, at different stages of rehabilitation, on the effects of auricular and body points combined, and the effects of EA with needles and surface electrodes and at different frequencies. Basic research studies should compare different schedules of administration to explore the cumulative effect and the duration of the effect, particularly if acupuncture is to be considered as a long-term intervention for reducing cravings during rehabilitation. Electrical stimulation in the form of TEAS has recently been studied. In an RCT, 48 participants entering an inpatient opioid detoxification programme received real or sham TEAS three times daily for up to 4 days. Abstinence was significantly increased in the treatment group. There was a trend towards a reduction of withdrawal symptoms but not craving.

Clinical studies should consider a wider range of outcomes than previously. Recruitment rates to programmes with and without acupuncture could be compared. Measures should be used for withdrawal symptoms and cravings as well as attrition, which is important in predicting recovery. Other psychological aspects of withdrawal should be measured to capture the whole experience. Some progress has already been made towards measuring the outcomes that are seen in clinical practice. In a naturalistic study, anger, concentration, sleep energy and pain management were measured over time in 367 inpatients. In an RCT, 67 veterans newly withdrawn from various drugs of dependence (mainly alcohol) were recruited. They were randomised to twice-weekly NADA acupuncture, relaxation or usual care. Measurements included craving, quality of life and spirituality. Forty-seven completed the study, and the acupuncture group scored a significantly greater reduction in craving scores than the usual care group but not the relaxation group. Anxiety scores were lower in both acupuncture and relaxation groups than in the usual care group.

### Table 2
Numbers of studies with positive and negative results for four different outcome measures and associated treatment variables (numbers or means as appropriate)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Abstinence</th>
<th>Attrition</th>
<th>Craving</th>
<th>Withdrawal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Totals*</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>25</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Mean N</td>
<td>48</td>
<td>175</td>
<td>143</td>
<td>185</td>
</tr>
<tr>
<td>Auricular</td>
<td>29</td>
<td>16</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Face</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Body</td>
<td>13</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Needles, n</td>
<td>47</td>
<td>4.6</td>
<td>7.5</td>
<td>6.6</td>
</tr>
<tr>
<td>Bilateral</td>
<td>20</td>
<td>9</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>EA</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Daily sessions</td>
<td>25</td>
<td>11</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Total sessions</td>
<td>48</td>
<td>20</td>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

*Number of studies providing data for each row.

EA, electroacupuncture.

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This paper has no direct implications for clinical practice since it generates no new evidence. It should be stressed that acupuncture can only be a part of multidimensional rehabilitation therapy. The NADA protocol, prominent in the West, is simple and economical to administer to large numbers in the acute setting and is highly valued by patients, giving them a sense of empowerment. It is also appreciated by carers and by the criminal justice system. There is some evidence to support it: four out of five comparisons of auricular acupuncture with non-acupuncture controls were positive and, although only 8/24 sham-controlled studies were positive, this low proportion could be explained by the use of active control.

In conclusion, the current evidence suggests that acupuncture may have some effects on drug dependence that have been missed in the outcomes measured in some previous studies. These need to be carefully addressed in future studies. Further research is justified into the effects of acupuncture at body points, EA and bilateral needling.

**Summary points**

- Acupuncture is used for drug dependency, despite lack of evidence.
- This review explored which aspects were associated with positive effects.
- Best results are for craving and withdrawal, using body acupuncture, electroacupuncture and bilateral needling.

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**REFERENCES**


