The Design of Clinical Trials in Irritable Bowel Syndrome using Acupuncture and Related Meridian Therapies

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Abstract
Current allopathic treatments for irritable bowel syndrome (IBS) are of limited efficacy. Complementary therapies, such as acupuncture, moxibustion, massage and cupping, including hijama, are frequently promoted in the lay press as effective alternatives. In addition, a number of clinical trials have been published, especially with regards to acupuncture, which indicate that they do have therapeutic benefits. This review considers the difficulties associated with formulating randomised controlled trials of such therapies and indicates approaches which may allow objective assessments of their effectiveness.

Keywords
Irritable bowel syndrome, Acupuncture, Moxibustion, Marma, Cupping, Hijama, Randomised controlled trials

Introduction
Randomised control double blind studies are generally accepted as the gold standard for assessment of therapeutic interventions as they provide both more control for bias as well as sound evidence of cause and effect. Such studies should also be the most suitable ones to measure the effect of traditional techniques, such as acupuncture or moxibustion. They should overcome issues related to the complexity of irritable bowel syndrome (IBS) and the difficulties associated with its definition as well as the nature of meridian therapies. Any trial should be designed so as to answer a clear question and that includes whether the treatments comparable or superior to the other treatments or a placebo.

Important Elements for Trials in IBS
Patients in an IBS trial need a clear and certain diagnosis. They should be representative of the population from which they are drawn, and ideally include ethnic minorities. In addition, the study should include sufficient patients to ensure that it is adequately powered to provide a reliable answer to the question being asked. Outcome measures need to be valid and reliable [1]. Changes in symptoms and their impact on daily life are the only outcomes which can be assessed in IBS. Of symptoms, pain is the most consistent, while its impact on time lost from work and resulting depression are all features which could be assessed, either by an external observer or through patient reported outcomes. The issue of bias can be addressed through randomisation and blinding of external assessors.

Design of Trials in IBS
Within the study design the control group can be one of six types according to the Food and Drug Administration [2] classification namely: Placebo concurrent controls, active-treatment concurrent controls, no-treatment concurrent controls, dose-comparison concurrent controls, external controls and multiple controls. Pharmacological treatments, such as mebeverine and peppermint oil, are in regular use in IBS and so the most suitable study design would be one with active-treatment concurrent controls. However, the comparison of tablet therapy with an intervention which includes significant interaction between patient and therapist may limit an assessment of the technique itself. Therefore, the introduction of a placebo concurrent control for an intervention, such as acupuncture, is ideally needed. However, there is an ethical issue related to the use of placebos where an effective alternative treatment exists. Under Article 32 of the Declaration of Helsinki [3] such an approach can be acceptable where for sound methodological reasons use of placebo is necessary to determine the efficacy of an intervention and patients who receive placebo will not be subject to any risk of serious harm.

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The importance of “blinding” was underlined by Day & Altman [4]. It is particularly important when the response criteria are subjective, such as relief of pain, which is the main outcome measure in IBS trials and is usually reported by patients. Patients are seldom blind to an active intervention, even when a sham treatment has been used. Schulz, et al. [5] have shown that inadequate concealment leads to a significantly larger estimate of treatment effect. In the case of interventions, such as acupuncture or moxibustion, concealment from patients is almost impossible.

The specific issues, in relationship to assessment of trials investigating the efficacy of acupuncture and related therapies in the management of IBS or their superiority/inferiority to allopathic treatments include assessments of:

1. The diagnostic criteria used to identify subjects for the trial
2. The method of selection of patients from amongst suitable subjects for inclusion in the trial
3. Randomisation procedures and whether they are transparent
4. If the study is placebo controlled, the nature of the placebo
5. The style of acupuncture and the type of moxa used
6. The skills of the practitioners
7. Details of blinding of patients, practitioners and assessors
8. The outcome measures used and whether they have been validated
9. The duration of the trial and follow-up
10. The number of participants and whether a power calculation was performed prior to initiation of the trial
11. Drop-out rates
12. Potential bias amongst the authors of the publication

This list was drawn up from published trials and a range of guidances, including Evans & Ildstad [6] and the Food and Drug Administration [2].

### The diagnostic criteria used to identify subjects for the trial

The diagnosis of IBS is based on symptoms as there are no objective laboratory-based tests which can identify patients with the condition. The critical symptoms for reaching a clinical diagnosis have been defined in two commonly used tools, namely the Manning [7] and Rome criteria [8]. The Rome criteria have gone through several revisions with Rome IV being the latest. Unfortunately, Manning and Rome criteria demonstrate significant differences when distinguishing case from non-case. In a comparative study using the criteria proposed by Manning and Rome I and II the prevalence of IBS in a community based study of 5000 people was reported as 16.2%, (Manning with only 2 symptoms) 9.7%, (Manning with 3 symptoms) 5.6%, (Rome I) and 5.1% (Rome II) [9]. Such differences are of considerable importance when selecting patients for treatment studies and are likely to affect outcomes. Intuitively, one would suspect that the stricter criteria of Rome II are most likely to identify patients more truly representative of IBS. In addition, Ford, et al. [10] demonstrated that the diagnostic value of Manning criteria was only modest in a systematic review of 10 studies involving 2355 patients. However, Rome II has now been replaced by Rome III and more recently Rome IV.

Published information on the criteria used to select patients in various trials of acupuncture and moxibustion is of variable standard. In a Pubmed search using the terms: Acupuncture, moxibustion, cupping, massage, clinical trials and human in various combinations and covering the period 1980 to 2018 of 66 papers identified, 25 concerned clinical trials or imaging studies. These 25 papers required a clear definition of IBS, but in 10 cases the original paper was in Chinese and the abstract did not provide such details. In the remaining 15 clinical trials diagnostic criteria were reported in 13 studies. In the remaining 2 studies, which were both from the UK, the diagnosis was based on unspecified clinical grounds (See Table 1 and Table 2) [11-25].

These papers were identified from a Pubmed search using terms acupuncture, moxibustion and massage and included papers investigating mechanisms of action and controlled

### Table 1: Publications in which the diagnostic criteria for identification of patients with IBS were stated.

| Procedure             | Criteria | China | Korea | North America | Europe | Middle East |
|-----------------------|----------|-------|-------|---------------|--------|-------------|
| Acupuncture           |          |       |       |               |        |             |
| [11]                  | Rome     |       |       |               |        |             |
| [12]                  | Rome 1   |       |       |               |        |             |
| [13]                  | Rome 1   |       |       |               |        |             |
| [14,15]               | Rome 2   |       |       |               |        | 1           |
| [16-19]               | Rome 3   |       |       |               |        | 1           |
| [20,21]               | Clinical |       |       |               |        | 2           |
| Moxibustion           |          |       |       |               |        |             |
| [22]                  | Rome 3   |       |       |               |        | 1           |
| Acupuncture/Moxibustion|         |       |       |               |        |             |
| [23-25]               | Rome 3   |       |       |               |        | 3           |
The nature of controls in IBS studies

In 2007 Dorn, et al. [26] reviewed 19 trials of complementary therapy in IBS where the placebo response rate was 42.6% (95% CI 38.0-46.5%). The placebo response rate did not correlate with the type of treatment or trial duration. However, it did correlate with duration of treatment and number of office visits. Such findings emphasised Vincent and Lewith’s [27] call for credible controls in any investigation of acupuncture and the potential impact of an “holistic” approach to care. Support for such a view also comes from a systematic review of the placebo effect of psychological interventions in the treatment of IBS, which had comparable response rates [28].

The creation of a credible placebo for acupuncture, moxibustion, massage and other complementary interventions is a significant challenge for researchers. Dorn, et al. [26] consider that the holistic approach taken by practitioners of complementary therapy cannot easily be separated into its component parts and, as Kaptchuk [29] has suggested, the “healing ritual” associated with such therapies may be a significant factor in their clinical outcomes. These factors are seldom reproduced in clinical trials and if they are may enhance the response to a placebo control.

The Design of Sham Acupuncture Procedures

There has been considerable confusion in the published literature between the terms “sham acupuncture” and “placebo needle”. Sham acupuncture should be used to refer to use of a non-penetrating needle whereas placebo needle should be used for the needling of recognised points concerned with different disease processes or of areas which are not acupuncture points [30]. However, the needling of wrong points concerned with other diseases raises serious ethical questions as to do so may produce adverse outcomes for the patient. In a systematic review of 38 trials which used placebo needle insertion at wrong points Moffet [31] found comparable responses to true insertion in only 2 cases, but the needle appears to have been inserted only superficially or minimally stimulated. He did not record any adverse outcomes. In a meta-analysis of 29 trials MacPherson, et al. [32] analysed non-needle sham, penetrating needles and non-penetrating sham needles. They found that acupuncture was significantly superior to all categories of control group. However, there was a smaller benefit from true acupuncture when the control was a penetrating needle. This supports the view that any form of actual needling, as opposed to sham needling, could be of clinical benefit. Interestingly in the trials reviewed by MacPherson, et al. [32] penetrating needles were usually inserted at locations close to true acupuncture points, rather than at other points. Some acupuncturists consider there to be an area of activity rather than a specific point. Consequently, needles placed close to an acupuncture point may have a comparable effect to insertion at the exact point.

Non penetrating needles

These are devices in which the needle retracts into the

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**Table 2**: Publications in which the diagnostic criteria for identification of patients with IBS were stated.

| Procedure                  | Language | Type of Study                                      | Number of Patients | Male/Female |
|---------------------------|----------|---------------------------------------------------|--------------------|-------------|
| Acupuncture               |          |                                                   |                    |             |
| [11] English RCT with sham acupuncture | English | RCT with sham acupuncture                          | 25                 |             |
| [12] English RCT with sham acupuncture | English | RCT with sham acupuncture                          | 79                 | 64 (81%)    |
| [14] English RCT with sham acupuncture | English | RCT with sham acupuncture                          | 43                 | 34 (79%)    |
| [15] English RCT with sham acupuncture | English | RCT with sham acupuncture                          | 153                | 153 (100%)  |
| [16] English RCT with sham and with mebeverine | English | RCT with sham and with mebeverine                  | 60                 | 49 (82%)    |
| [17] English Randomised investigation of neurological effects of acupuncture | English | Randomised investigation of neurological effects of acupuncture | 30                 | 15 (50%)    |
| [18] Chinese RCT with pinaverium | Chinese | RCT with pinaverium                                | 63                 |             |
| [19] English RCT with sham acupuncture | English | RCT with sham acupuncture                          | 42                 | 42 (100%)   |
| [20] English Open study of acupuncture alone | English | Open study of acupuncture alone                    | 7                  |             |
| [21] English RCT of acupuncture compared to standard treatment | English | RCT of acupuncture compared to standard treatment | 233                | 188 (81%)   |
| Moxibustion               |          |                                                   |                    |             |
| [22] English Randomised investigation of neurological effects of acupuncture | English | Randomised investigation of neurological effects of acupuncture | 33                 |             |
| Acupuncture/Moxibustion   |          |                                                   |                    |             |
| [23] English Randomised comparison of neurological effects of acupuncture and moxibustion | English | Randomised comparison of neurological effects of acupuncture and moxibustion | 60                 |             |
| [24] English RCT of acupuncture compared to moxibustion | English | RCT of acupuncture compared to moxibustion        | 85                 |             |
| [25] English RCT of acupuncture compared to moxibustion | English | RCT of acupuncture compared to moxibustion        | 82                 | 51 (62%)    |

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handle rather than penetrating the skin. For them to be valid placebos, patients should be unable to distinguish them from true needles. However, the pressure of the needle against the skin is said to give a sensation like insertion. One study of 80 volunteers found 33% were able to distinguish a true needle from a non-penetrating needle [33]. The validity of non-penetrating needles is further brought into question by the work of Takakura & Yajima [34]. In their study 20 of 60 non-penetrating needle applications produced the sensation of *deqi* compared to 48 of 60 penetrating needle insertions. *Deqi* is regarded as the sign of effective acupuncture needling in traditional acupuncture. It is, therefore, possible that sham needling in these studies was effectively the same as real needling. Further concerns about sham acupuncture have been raised by a Korean study of 79 acupuncture-naive and experienced volunteers. There was some evidence that previous knowledge and experience of acupuncture increased the likelihood of being able to distinguish true from sham needling [35].

**No needle sham**

In general, the size of the effect difference between true acupuncture and sham needle acupuncture is relatively small. In contrast when compared to an active control group the effect is often moderate and clinically relevant. One intermediate approach is to use techniques such as an inactivated laser or transcutaneous electric nerve stimulation (TENS) device. In a German trial of 177 patients with chronic neck pain sham laser acupuncture was as effective as real acupuncture but both were significantly more effective than western massage [36].

**The Design of Sham Moxibustion Procedures**

Sham moxibustion devices first became available in 2006 [37]. The initial trial was in moxibustion naïve volunteers, who consequently were unaware of the warm sensation experienced with moxa at the site of application. The sham device incorporated an insulating plate at the base to prevent heat reaching the acupuncture point. Consequently, this apparatus was not suitable for use in trials where patients were included who had experienced treatment with moxa in the past. A recent modification has introduced pores into the insulating plate to allow release of some heat but such that the levels are below the normal therapeutic range of 42-44 °C [38]. However, as with sham acupuncture needling it is likely that this will have some therapeutic effect. In fact, work on the infrared (IR) spectrum and irradiance of different types of moxa sticks has shown that only a small proportion of the IR radiation emitted by them might affect subepidermal tissue. It appears that the thermal actions of moxa sticks are caused primarily by superficial effects on the skin and so it is impossible to separate the effects of moxa sticks from the sensation of heat [39]. Overall, it appears that it is unlikely that a credible sham placebo for moxa therapy will be developed in the near future and so trials should compare moxa therapy with other treatments.

**The Design of Sham Marma Procedures**

There have been no published trials which have compared Marma therapy with Sham Marma. Indeed, there have been few trials which have compared any form of massage with sham massage. One of the few examples was in a study of structured Swedish style therapy compared to light touch body work in patients undergoing chemotherapy. By its nature, neither therapists nor patients were blind to the procedure and at the end of the study there were no significant differences in patient satisfaction [40]. The role of touch was recognised in the 1980s by Norman Autton as an important aspect of interaction, especially involving communication of love and security [41]. In a study of 22 patients, 13 of whom had IBS, 10 found that healing sessions made them feel more relaxed and 7 described feelings of warmth from the therapists’ hands even without contact [42]. Such subjective sensations may contribute to the ritualistic effect of acupuncture [29] and also of marma.

As with moxibustion, it is difficult to see how an effective placebo to marma could be developed as simple touching is recognised to have therapeutic benefits. However, a recent study of bypass patients in Rafsanjan showed that acupressure was significantly more effective at reducing pain severity in the intervention group than simple touching without pressure at the same points in the control group [43]. The applied pressure was about 3 -5 kg in the acupressure group and patients were described as feeling warmth, numbness, and weight, but in the control group, the touch was applied without pressure. The assessor of pain was blinded to which treatment had been administered, but the control intervention lacked the characteristics of acupressure and so would appear at first not to be an ideal sham.

**The Design of Sham Hijama Procedures**

Hijama or wet cupping has been investigated in a limited number of trials where it has been compared with other interventions [44]. However, there have been no trials of sham hijama. This contrasts with dry cupping, where a Korean group has developed a placebo cupping jar which can be attached to the skin without any negative pressure inside the jar, although the sham cup did not produce the characteristic weal [45,46]. In a German randomised controlled study of 141 patients where sham cupping was described to participants as “gentle cupping” compared to “traditional cupping” both groups experienced significant benefit compared to those receiving conventional therapy.

**Conclusion**

Comparative studies have either exposed patients to an active intervention and compared the outcome to a group receiving a placebo or looked at two treatments for IBS and compared outcomes. In the case of IBS the ethical issues related to use of placebos can be addressed by ensuring both intervention and control group receive standard allopathic therapy throughout the trial and evidence is sought that the intervention conveys added benefits. The disadvantage of such an approach is that any added benefit may only be marginal and so would require much larger trials in order to ensure significance is achieved.

However, all trials concerned with treatment in IBS need
to ensure that patients have a robust diagnosis supported either by Manning or Rome criteria. When an intervention such as acupuncture is under investigation the preferred design would be to include both a sham intervention and an effective other therapy such as peppermint oil capsules or mebeverine. Credible sham interventions present significant challenges to researchers as they may not be inert either because they stimulate acupoints or through a ritualistic effect.

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