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Ultramolecular homeopathy has no observable clinical effects. A randomized, double-blind, placebo-controlled proving trial of Belladonna 30C

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Aims To investigate if ultramolecular homeopathy has any clinical effects. This was assessed using the proving of the homeopathic remedy Belladonna given at an ultramolecular dose (30C), as a model. A proving states that when a homeopathic remedy is given to a healthy person, they will experience symptomatic effects specific to that remedy. If ultramolecular doses are clinically active, the Belladonna 30C group should experience more true Belladonna proving symptoms than the placebo group.

Methods Healthy subjects ($n = 253$), aged 18–30 years, took part in this double-blind, randomized placebo-controlled study. Total study duration was 4 weeks. Subjects were randomized before 1 week placebo run-in. They received 2 weeks of treatment intervention (Belladonna 30C or placebo) and were followed up for 1 week. Subjects recorded any symptoms experienced during the total study period on a daily basis using a structured questionnaire. Symptom diaries were analysed blind to determine if each subject had proved or not (based on predefined criteria). The main outcome was the proportion of subjects who had proved in each treatment group.

Results No significant group differences in proving rates were observed [Belladonna provers $N = 14$ (13.9%); placebo provers $N = 15$ (14.3%); mean difference −0.4%, 95% confidence interval −9.3, 10.1] based on intention to treat analysis. Primary outcome was not affected by seasonality or the individual's attitude to complementary medicine.

Conclusion Ultramolecular homeopathy had no observable clinical effects.

Keywords: homeopathy, randomized controlled trial, ultramolecular

Introduction

The use of homeopathy is increasing [1–3] with 1.2% of the UK population visiting a homeopathic practitioner each year and 8.5% purchasing over the counter homeopathic remedies (4). The most contentious issue within homeopathy is the practice of prescribing very low or ultramolecular doses of remedies. Homeopathic potencies [usually a dilution of 1 : 10, decimal (D) or 1; 100, centesimal (C)] are made by a process of serial dilution with succussion (shaking) between each dilution. Any dilution greater than 10^{-24} (12C) is below the Avogadro number and is ultramolecular. Clinically and in research trials, the most commonly used homeopathic potency is an ultramolecular potency of 30C (the solute undergoes 30 serial centesimal dilutions with succussion). No definitive mechanism has been identified to explain how these ultramolecular dilutions may act, although several theories have been proposed [5–7]. A meta-analysis [8] and three systematic reviews [9–11] suggest that in 'good' quality trials, homeopathy has a significantly greater effect than placebo [8–10], although the strength of the effect is disputable [11] and engenders much debate.

Homeopathic pathogenetic trials (or 'provings') are used as a model to investigate if ultramolecular dilutions

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have any clinical effects in healthy volunteers. Homeopathy states that a substance made in a homeopathic dilution will produce a characteristic set of symptoms when taken by healthy individuals; this is known as a 'proving'. Homeopaths match the set of symptoms that the patient presents when they are ill, to these proving symptoms, to enable them to make their prescription on the basis of 'like cures like'. Proving symptoms form the basis of the homeopathic materia medicas and therefore provide the clinical basis for all homeopathic prescriptions [12–14]. Experimental proving trials have varied considerably in their methodology but almost all are of poor quality [15] and scientific re-evaluation of the original data is needed [16–21] to confirm that the remedy-specific symptoms recorded in the proving trials (and hence the material medicas too) can be independently replicated [22].

Belladonna, in a homeopathic dilution, is an acute remedy associated with head and upper respiratory tract symptoms, and inflammation. There have been several reproving studies of Belladonna [22–26]. The first proposal for a double-blind, placebo-controlled trial designed to 're-prove' Belladonna, published in 1906 [23], employed the traditional proving method where subjects are interviewed each day to obtain a detailed symptom diary [24, 25]. Walach subsequently investigated the effects of Belladonna in a series of studies [22, 26–28] in which he developed [27] and then employed a novel approach using a closed questionnaire [22, 27] which contains both true and false Belladonna symptoms. Goodyear, Lewith and Low [28] further developed the Walach model to include an open section to record other symptoms and developed a definition of a proving reaction. Three studies have employed the questionnaire approach using Belladonna [22, 27, 28] and significant group differences in proving rates have been identified when the primary outcome is based on the proportion of individuals experiencing a proving reaction [27, 28]. The issue of inadequate power highlights the need for a large-scale study.

The aim of this study was to investigate whether ultramolecular homeopathy has any clinical effects. This was achieved by investigating whether an ultramolecular dilution of Belladonna 30C could be differentiated from an identical placebo in the context of a proving trial, by comparing individual proving reactions between Belladonna 30C and placebo. This study was based on the previous pilot [28].

Methods

Design

The study was a double-blind, randomized parallel group, placebo-controlled trial.

Recruitment

Ethical approval was sought and granted by Southampton and South-west Hampshire Ethics Committee (LREC 363/00) and the East Dorset Local Research Ethics Committee (LREC 97/01/S). Student volunteers were recruited locally (November 2000 to December 2001).

Inclusion and exclusion criteria

Inclusion criteria were: aged 18–35 years, with stable, good health (screened by questionnaire). Exclusion criteria were: use of medication (conventional, herbal or homeopathic) in the previous 4 weeks (contraceptive pill and occasional use of painkillers was acceptable); acute or intercurrent illness on entry; illness during the study requiring excluded medication; current/possible pregnancy or lactation.

Medication, randomization and blinding

An independent homeopathic dispensary, Ainsworth Homeopathic Pharmacy (London, UK) prepared, in identical bottles, the placebo and Belladonna 30C medication, in accordance with the Blackie Foundation guidelines [29]. Placebo medication underwent the same preparation as Belladonna 30C, without containing Belladonna. The randomization schedule was prepared by an independent statistician using computer-generated random numbers with stratification (gender, medical knowledge). The randomization coding was held by the independent study homeopath in a sealed envelope until data entry and analysis was complete; the code was broken only for serious adverse events. Subjects were blinded to the placebo run-in phase and that the medication was Belladonna 30C. The Belladonna 30C and placebo tablets were assessed for quality of matching by an independent panel (MRC Clinical Trials Unit) and found to be indistinguishable. Subjects and investigators were asked to guess their treatment at study completion to assess blinding.

The proving questionnaire

The primary outcome was based on a proving response as identified by the proving questionnaire (PQ). The PQ (see Table 1) contained 12 statements with an 'open' section for subjects to record other symptoms. These statements included: (i) five true Belladonna symptoms selected from valid homeopathic reference source [30]; (ii) five false symptoms; and (iii) two statements for internal consistency. Symptoms recorded in the 'open' section were coded as true of false [30].

Table 1 Symptoms used in the proving questionnaire.

True Belladonna symptoms
1 My lips are inflamed
2 I have experienced shooting, tearing pains in my lower limbs, that are made better by walking
3 I had an unusual dry racking cough after 11 pm
4 I have a sinking and rising sensation in my head
5 My pupils are unusually dilated, especially when I feel hot
False Belladonna symptoms
1 I enjoyed listening to my favourite music station today
2 My ears feel as if they are frozen, regardless of the weather
3 I have had an unusual fear of crowds
4 I have a stitching pain in my fingertips when I grasp something
5 Everything tastes bitter except for water
Two statements for internal consistency
1 My lips feel like they have shrunk
2 I have disliked all music today

Study procedure

At baseline, informed consent and the subject's medical history, current health and their attitudes to complementary medicine [31] were recorded. Subjects were randomized and entered into the 4-week study (placebo run-in week, 2 treatment weeks and 1-week follow-up). The study medication was taken twice daily, within the same 2-h time period each day and subjects were asked to avoid factors that may render the medication inactive. In accordance with homeopathic practice, the medication was taken sublingually without touching the tablets. Subjects recorded, daily during the 4-week study, any new symptom that could not be attributed to any other cause, or any exacerbation of pre-existing symptoms, on the PQ. Illness days, medication use, missed or late doses of the trial medication, and intake of alcohol and cigarettes were recorded on a daily basis. Subjects were telephoned weekly to monitor adverse events, to aid compliance and to ask subjects to withdraw if they had taken any recreational drugs. At the end of the study both subject and investigator 'guessed' the subject's treatment group. Subjects received a nominal sum for travel expenses (£10).

Outcome measures

The primary outcome measure was an individual proving reaction to Belladonna 30C based on the following proving definition defined during the pilot study [28].

Proving is defined as at least two true symptoms on at least 2 consecutive days with no more than one false symptom during the 21 days of the study period. If an individual experiences an intense proving reaction (i.e. experiences a severe symptom(s) that is associated with Belladonna) and therefore has to withdraw from the study, this will still be considered to be a proving reaction even though they have not completed the data collection for 21 days (provided the remaining criteria for proving have been met). A proving reaction may include either predefined true symptoms or symptoms that are spontaneously recorded (according to Synthesis, 1999 [30]).

Secondary outcomes were: (i) whether seasonality affected proving response; (ii) whether proving response was associated with a positive or negative attitude to complementary medicine; and (iii) adverse event reporting was also described.

Statistical analysis

The sample size, based on the pilot [28], was designed to identify a 10% (absolute) difference in individual proving between treatment groups allowing for a 35% drop-out rate. The power calculation identified that 132 subjects per group were required (or 180 subjects per group incorporating the drop-out rate) based on 80% power and 5% significance. The data were analysed on an intention to treat basis. A symptom was counted as present on each day that the appropriate box was ticked during the 28 observational days. Each individual's outcome (prover or nonprover) was determined blind prior to breaking the randomization code. Differences between the Belladonna 30C and placebo group were assessed by comparing the proportion of provers in both groups using the χ^2 test or Fisher's exact test. Confidence intervals are quoted at the 95% level.

Results

Two hundred and six subjects completed the study (Figure 1). Recruitment was biased to those subjects studying medically related courses (medical $N = 145$, nonmedical $N = 61$), specifically female medical subjects (56.3% of the total population). Baseline measures were balanced at entry (Table 2) with no significant differences between treatment groups. All subjects were in good health (90% were symptom free) and free from any excluded medication at study entry, and there was no group difference in daily intake of alcohol or cigarette intake. The process of blinding was deemed to be secure for both the investigator ($\chi^2 = 2.26$, DF = 2, $P = 0.323$) and the subjects ($\chi^2 = 0.76$, DF = 1, $P = 0.382$). In addition, as the rate of inconsistent data reporting was <0.001%, we concluded that the data were reliably recorded.

Primary outcome

The numbers of provers classified during the placebo run-in and the treatment phase per treatment group are shown in Table 3. Based on our predefined criteria, 29

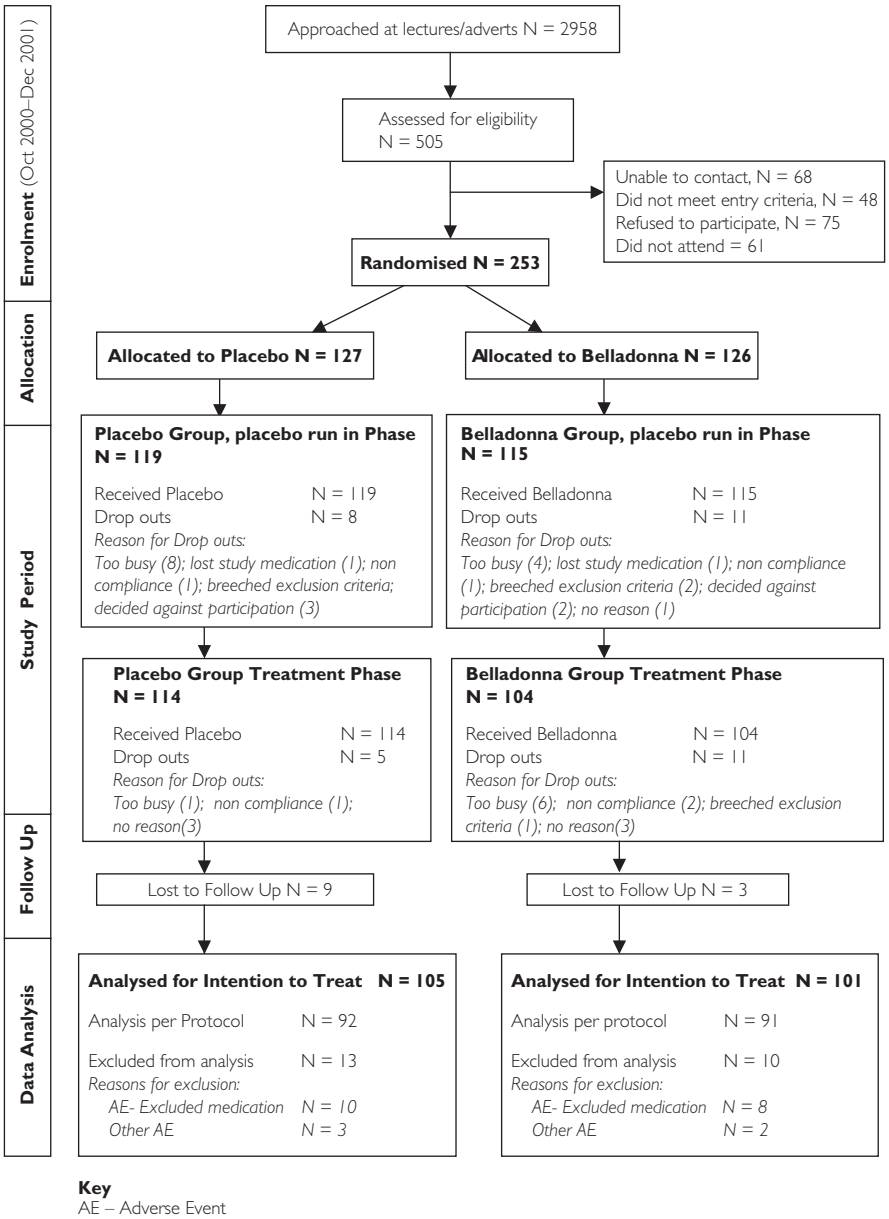

Figure 1 Consort Diagram.

subjects proved during the treatment phase. No significant difference in proving response between the Belladonna 30C-treated group compared with placebo was identified; group difference in provers was a negligible −0.4% [95% confidence interval (CI) −9.3, 10.1].

Secondary outcomes

Does seasonal variation affect proving response? The symptoms associated with Belladonna 30C may be seasonally dependent, so the effect of season on proving response was investigated. No association was identified ($\chi^2 = 3.03$, DF = 3, $P = 0.387$).

Does attitude to complementary medicine affect proving response? There was no evidence that either a positive or negative attitude to complementary medicine was related to proving response.

Adverse event reporting Due to the nature of the study, symptoms reported in the open section of the proving questionnaire could be part of the proving response or considered an adverse event. Adverse events (AE) were defined [32] as those symptoms that (i) resulted in subjects taking excluded medication (i.e. non-Belladonna-related medication) to alleviate their effects; or (ii) were true symptoms that led to the subject withdrawing from the study; or (iii) were any false symptom that required excluded medication. Thirty-seven AEs were reported, including two serious adverse events (SAE) requiring inpatient hospital (one Belladonna C30-treated, the other placebo). The verum subject experienced undiagnosed

Table 2 Baseline group measurements.

Baseline measure	Belladonna group (N = 101) Mean	SD	Placebo group (N = 105) Mean	SD
Age (years)	22.5	3.80	22.0	2.20
Sex (F : M)	78 : 23 (77.2% : 22.8%)		86 : 19 (81.9% : 18.1%)	
Body mass index	22.2	2.65	22.7	3.20
Contraceptive pill users (%)	42.6		45.7	
Attitude to complementary medicine*	41.6	7.02	41.3	7.65
Smokers (%)	13.9		12.4	
Cigarette consumption, no. per day	5.8	4.00	5.0	2.24
Daily caffeine intake (cups)	2.3	2.02	2.34	2.35
Weekly alcohol intake (units†)	8.4	7.01	9.3	7.45
Subjective health score‡	2.1	0.66	2.2	0.81

*The Attitudes to Complementary Medicine Questionnaire which gives an overall single score ranging from 14 to 84, with a lower score indicating a pro CAM attitude. †One unit of alcohol is equivalent to half pint of beer lager or one glass of wine or one measure of spirit. ‡Assessed by a six-point Likert scale where 1 = excellent health and 6 = very poor health.

Table 3 Primary outcome: provers identified in the placebo run-in and treatment phase.

Study phase medication	N assessed proven	Difference (95% CI)	n (%)
*Run-in phase**			
Belladonna	101	8 (– 6.3, 9.0)	1.2 (7.9%)
Placebo	105	7	(6.7%)
Treatment phase			
Belladonna	101	14 (– 9.3, 10.1)	– 0.4 (13.9%)
Placebo	105	15	(14.3%)

*All subjects received placebo during the placebo run-in period.

severe abdominal pain in the upper right quadrant (which could be a Belladonna-related symptom); the placebo subject was admitted with pancreatitis. Both subjects made a rapid recovery. There was no significant difference in AE reporting between either the treatment groups, or between provers and nonprovers.

Discussion

If ultramolecular dilutions have clinical effects, an increased proving response should be observed in the Belladonna 30C group, as suggested by the pilot [28]. No group differences in proving rates were identified (and this was additionally borne out using alternative definitions of proving) which confirms that there is no support for any clinical effect of ultramolecular homeopathy within this model. The baseline data showed that the two treatment groups were balanced. We identified total proving rates of 14%, similar to those found in traditional proving studies (e.g. [33, 34]), which suggests that the PQ appears to be sensitive enough to detect proving, and we confirmed that the data were completed reliably. The blinding was secure and covariates were shown to have no effect on outcome.

This is the largest double-blind randomized controlled trial ever conducted for homeopathic proving. Due to difficulties in recruiting, we were unable to meet our recruitment target (206 subjects completed *vs.* the 264 required) which may generate a Type II error. Our data were powered to detect a 16% (absolute) group difference in individual proving rates, which would be consistent with previous proving studies comparing homeopathy and placebo [33]. No positive trend was identified in the Belladonna-treated group, so our conclusion that ultramolecular homeopathy has no effect over placebo is warranted. Previous homeopathic clinical trials (e.g. Reilly *et al.* [35] and Lewith *et al.* [36]) seem to demonstrate that encouraging pilot data cannot be confirmed in larger definitive trials. This study has raised a number of questions. Proving studies form the basis for homeopathic prescribing, yet these data have not provided evidence for the existence of a homeopathic effect using a commonly prescribed remedy. It could therefore be suggested that the central tenets that underlie homeopathy are not valid, i.e. the concepts of provings and ultradilutions, which has considerable implications in terms of homeopathic practice. It is also possible that the methodology employed to investigate these concepts is inadequate. The essence of homeopathy lies in its individualized treatment and it could be that this quantitative approach is not the most appropriate tool. Further methodological concerns include: (i) the sensitivity of the proving definition. The verum subject experienced severe Belladonna-type symptoms that resulted in a SAE but was not classified as a prover as she experienced two false symptoms, the criteria only allowing one false symptom;

(ii) young healthy subjects were recruited as they would be good responders but their consumption of alcohol and possible undisclosed recreational drug intake may minimize any homeopathic response. Lifestyle factors may colour the outcome, e.g. Belladonna-related symptoms of 'headache' and 'sinking and rising sensation in his head' were reported following high alcohol intake the previous evening.

Despite this being a clearly negative study for homeopathy, surveys confirm that patients use and continue to use homeopathy [2], and feel satisfied with their treatment [37]. Therefore future research should focus on the ideal approach through which to study homeopathy, with a shift towards understanding those factors such as the therapeutic relationship and the process of the homeopathic consultation [38, 39] that may mediate the apparent success of the homeopathic process.

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