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ORIGINAL PAPER

Depression treated by homeopaths: a study protocol for a pragmatic cohort multiple randomised controlled trial

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Background: **The most commonly recommended treatments for depression are psychological/psychotherapeutic treatments, and antidepressant drugs. However, 38 percent of patients with depression do not use these recommended treatments. Some patients seek homeopathic treatment for depression, but insufficient evidence exists to conclude as to the effectiveness, cost-effectiveness and safety of treatment by homeopaths for patients with depression. The aim of this trial is to evaluate the acceptability and comparative clinical and cost-effectiveness of the offer of adjunctive treatment provided by homeopaths for patients with self-reported depression.**

Method: **This pragmatic randomised controlled trial is embedded within the population based South Yorkshire Cohort (SYC) of whom nine percent self-report long-term depression. The SYC is designed to facilitate 'cohort multiple' randomised controlled trials (cmRCT). A self-completed questionnaire will be used to both screen and collect baseline data from potential trial participants. The primary outcome is PHQ-9. One-hundred-and-sixty-two participants will be randomly selected to the intervention group (Offer of treatment by a homeopath). The results of the Offer and the No Offer groups will be compared at 6 and 12 months using both an intention to treat (ITT) and complier average causal effect (CACE) analysis. Cost-effectiveness analysis will involve calculation of quality adjusted life year (QALY). In order to help interpret the quantitative findings a selection of up to 30 patients in the offer group will be invited to participate in qualitative interviews after the first consultation and after a minimum of 6 months. Interviews will be assessed by two researchers and results will be analysed using thematic analysis. Triangulation will be used to combine results from qualitative and quantitative methodologies at the interpretation stage, to see if results agree, offer complementary information on the same issue or contradict each other.** *Homeopathy* (2014) **103**, 147–152.

Keywords: Homeopathy; Depression; Cohort multiple randomised controlled trial; Effectiveness; Cost-effectiveness; Qualitative study; Mixed method

Background

Depression is the leading cause of burden of disease in middle- and high-income countries, with over 150 million people in the world suffering from unipolar depressive disorders.[1] Depression is also associated with considerable comorbidities.[2] In the UK, depression is the second largest contributor to disability adjusted life years.

The most commonly recommended treatments in the UK are psychological/psychotherapeutic treatment for minor to moderate depression, and antidepressant drugs for persistent and more severe depression.[3] The prescription of antidepressants in England increased by 9.1% from 2010 to 2011, with 46.7 million prescriptions issued.[4] Some systematic reviews suggest that antidepressants are

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effective, with small effect sizes[5], while others report that antidepressants have no effect in mild and moderate depression,[6] little effect on remission[3] or only borderline effectiveness,[7] or are only effective in more severe depression. Antidepressants are also known to cause significant side-effects[8]. Although antidepressant maintenance treatment has been found to be effective in many patients 17−30% still experience relapse of their depression symptoms over a 1−3 year period.[9]

Psychological and psychotherapeutic treatments such as cognitive behavioural therapy (CBT), counselling, interpersonal therapy, and psychodynamic approaches are recommended for mild to moderate depression by the National Institute for Health and Care Excellence (NICE) in the United Kingdom, but these recommendations are based on a limited number of depression trials, thus limiting the validity of their conclusions.[3] Effect sizes for such treatment modalities have also been found to be small.[10] As many as 38% of patients with depression are not using recommended treatments.[3]

Depression is one of the five most common reasons why patients use complementary and alternative therapies[11] and one of the main reasons why patients consult with homeopaths, both within the UK[12] and outside the UK[13].

Homeopathy is provided in some publicly funded healthcare systems and has been provided continuously in the UK publicly funded healthcare system, the National Health Service (NHS), since its inception in 1948. The first principle in homeopathy is treating 'like with like',[14] i.e. a substance that causes certain symptoms in healthy people may cure the same symptoms in those who are ill. The second (and more controversial) principle, is the process of serial dilution and succussion carried out to reduce risk of side effects and to maintain the medicinal properties of homeopathic medicinal products (HMPs). HMPs are European Union registered through a special simplified registration procedure.

Reviews of systematic reviews assessing the evidence base for homeopathy in any type of medical condition reach varying conclusions: no overall strong evidence in favour of homeopathy,[15] clinical evidence supporting the effectiveness and safety, but not the cost-effectiveness of homeopathy,[16] and positive (but not convincing) results in most trials.[17] Reviews of the evidence of the safety indicate that HMPs may cause mild transient side-effects, but not strong or persisting side-effects.[16]

In observational studies, fifty to eighty percent of patients receiving treatment from homeopaths for depression report at least moderate improvement.[18−23] A single double-blinded placebo-controlled randomised trial to assess the efficacy of HMPs found that individually prescribed HMPs were non-inferior to fluoxetine at 4 and 8 weeks of treatment.[24] A limitation of this trial was however high attrition rates. Two double-blinded placebo-controlled trials testing the efficacy of individually prescribed HMPs both failed to recruit sufficient numbers of participants, preventing analysis of results[25] or resulting in premature ending of the trial.[26]

No pragmatic randomised controlled trials (RCTs) of the real world effectiveness and cost-effectiveness of treatment by homeopaths for depression have been conducted. There is a need for high quality clinical trials which can inform clinical practice and commissioning, and innovative methodologies to address the challenges of recruitment. This trial does not aim to assess the efficacy of homeopathic medicines, but the effectiveness of a total 'package of care'. The trial has high external validity and thereby advances the field by providing evidence on the extent to which treatment provided by homeopaths in 'real world practice' in addition to usual care is of benefit to patients self-reporting depression compared to usual care alone.

Aims

The aim of this trial is to evaluate the acceptability and the comparative clinical and cost effectiveness of the offer of adjunctive treatment provided by homeopaths for patients with self-reported unipolar depression in addition to usual care, compared to usual care alone.

Methods and design

This study uses the 'cohort multiple' RCT (cmRCT) design[27] with participants recruited from the population based South Yorkshire Cohort (SYC) cohort, a large observational study and multiple trials facility. Over 27,000 patients have been recruited to the cohort from 41 GP practices in South Yorkshire and have provided baseline data on a range of socio-demographics, socio-economics, comorbidities (including depression), health resource use and health related quality of life (HRQoL). Over 22,000 participants have given consent to be contacted by researchers again and for their data to be used comparatively, and 89% of these participants have given consent to access their routine health records. Baseline data will facilitate the screening process, and minimise the time spent on recruitment.

Nine percent (n = 2000) of SYC participants self-report long-standing depression. These 2000 patients will be sent a screening and baseline data collection questionnaire (including the primary and secondary outcome measures). In case of insufficient response, questionnaires will also be sent to participants who reported suffering from anxiety or depression on the day of completing the questionnaire, adding up to a total of 5700 participants.

Inclusion criteria

Eligible trial group participants must be aged 18−85 and have a minimum baseline PHQ-9 score of 10 points, including scoring 2 points for either question 1 (little interest or pleasure in doing things) or question 2 (feeling down, depressed, or hopeless). A threshold of 10 suggests moderate level of depression and is considered the limit for clinically relevant depression.[28]

Exclusion criteria

These are kept to a minimum in order to maximise the external validity of the trial and include: no current or past diagnosis of bipolar disorder, Alzheimer's disease,

organic brain damage, schizophrenia, schizoaffective disorders, other psychotic disorders, or antisocial personality disorder; no homeopathic treatment over the past 3 months; and no current participation in another trial.

Randomisation

A random selection of those participants who meet the inclusion/exclusion criteria will be offered treatment by a homeopath. A person not involved in treatment or assessment of participants will use a random number generator in order to randomly select the Offer Group. The randomisation code will only be broken when the trial has been completed. Those not randomly selected to the Offer Group (No Offer Group) will act as a virtual control group. A flow-chart of the project is presented in Figure 1.

Outcome measures

The primary outcome measure is the Patient Health Questionnaire (PHQ-9) at 6 months. Patient reported outcome measures (PROMs) such as PHQ-9, where patients fill in questionnaires independently of a practitioner, researcher or assistant, are increasingly used in both depression research and clinical practice. PHQ-9 items correspond to DSM-V diagnostic criteria for depression. Secondary outcome measures include PHQ-9 at 12 months, and at 6 and 12 months: GAD-7, which tests levels of anxiety, the most common comorbidity in depression; and EuroQol (EQ-5D) to assess the cost-effectiveness of treatment.

Intervention

This trial will assess an Offer of treatment by a homeopath in addition to usual care, compared to usual care alone. Usual care may consist of nothing or any treatment patients are currently receiving, such as medication and consultations provided by patients' GPs, psychiatrists, psychologists or other healthcare workers. In regular practice, patients most often seek help from homeopaths after already having been offered or received some sort of established treatment.

In order to maximise the external validity of the trial, homeopaths are free to provide treatment as they do in everyday practice. Treatment by homeopaths includes an in depth consultation, the prescription of individually tailored homeopathic remedies, and sometimes advice to patients regarding diet, exercise, etc. No restrictions are put on the frequency and length of consultations. Practitioners will be paid a maximum of £ 250 per patient. The treatment period will last a maximum of 9 months.

Statistical methods

The primary outcome measure is the PHQ-9 score at 6 months. The level of significance (alpha error) is set to 0.05 and the power to 80%. The effect size used for the sample size calculation is set to 0.35. We estimate that 40% of SYC participants reporting long-term depression will return baseline screening questionnaires. The expected drop-out rate during the trial is 40%. Using unequal sample group size calculation (1:2 ratio for Offer: No Offer) gives a final sample size of 485, with 162 in the Offer Group and 323 in the No Offer Group. The unequal ratio used for sample size calculation contributes to reduced costs and increasing the power of the trial.

An intention-to-treat-analysis will be carried out, only excluding patients who withdraw their consent. Statistical exploratory tests will be two-tailed with alpha = 0.05. Baseline demographic (age, gender) and health related quality of life data (PHQ-9, GAD-7, EQ-5D, body mass

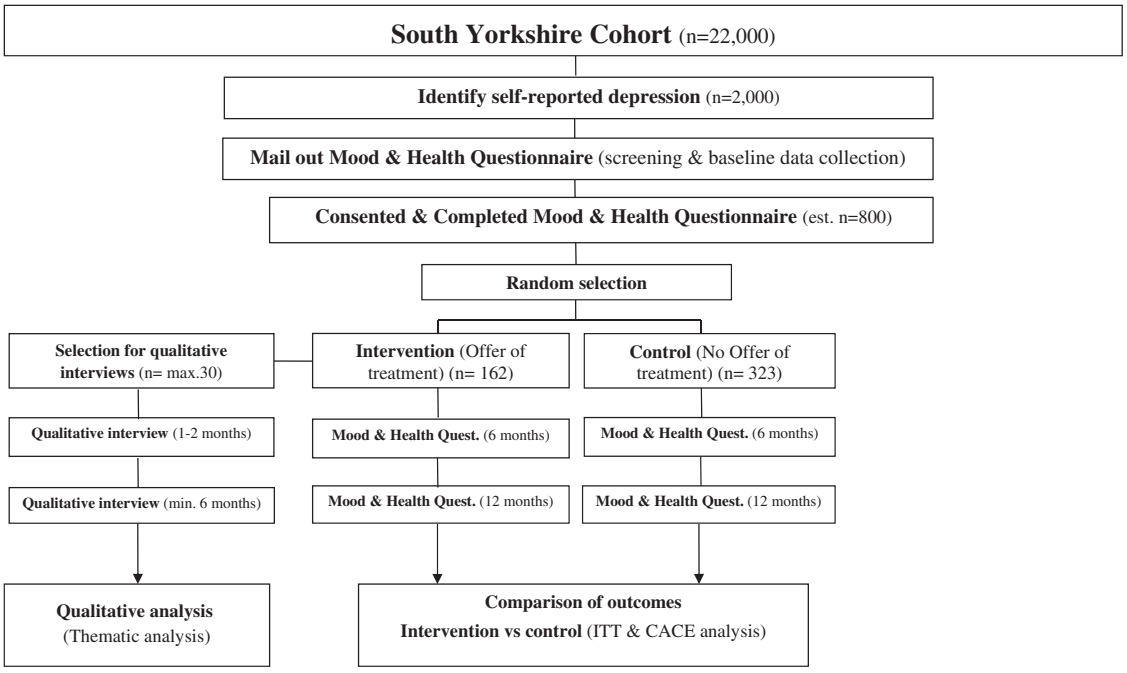

Figure 1 Project flow-chart.

index) will be assessed for comparability between the Offer and No Offer groups. The primary analysis will compare mean PHQ-9 scores at 6 months post-randomisation between the Offer and No Offer groups and will include 95% confidence intervals (CI). An adjusted analysis will also be performed alongside this unadjusted analysis which will include baseline covariates, such as age, gender and quality of life. Secondary outcomes, PHQ-9 at 12 months and GAD-7 and EQ-5D at 6 and 12 months post-randomisation, will be compared between the Offer and No Offer groups. A 95% CI for the mean difference in these parameters between the Offer and No Offer groups will be calculated.

For the primary outcome, the PHQ-9 score at 6 months post-randomisation, missing data will be imputed through a variety of methods, including Last Observation Carried Forward (LOCF), regression and multiple imputation. Data will be analysed using SPSS for Windows (version 20).

In addition, the complier average causal effect (CACE) will be assessed to consider the effect on participants who received treatment, as intended according to group allocation. CACE analysis is useful for assessing effects of treatments in RCTs with non-compliance and attrition, and provides a more robust analysis than per-protocol analyses.[29,30] For this purpose, it will be assumed that patients' decision not to accept the treatment offer will not affect outcomes.

A cost-effectiveness analysis will be carried out assessing the incremental cost-effectiveness ratio (ICER) and the incremental cost per quality adjusted life year (QALY) to compare the cost-effectiveness of treatment alternatives. The societal perspective will be used, and the target audience is patients, health care providers, employers and the NHS. Sub-group analyses include groups of depression severity and identified groups of various forms of usual care treatment. Analyses with project costs include treatment (medication and consultations) and other costs (patients' travel expenses), minus costs of averted disease and costs of averted loss of productivity: Cost of program − (cost of averted disease + cost of averted loss of productivity). Loss of productivity will be measured by counting work sick-leave (percentage and duration of days). As recommended by NICE, evaluation will include quality of life assessment, with utility measures based on EQ-5D to enable QALY calculation. The analytic horizon will include the entire study period (12 months).

Qualitative study embedded within the project

No qualitative research has been conducted assessing depressed patients' experiences with treatment provided by homeopaths. Therefore, in order to compare patients' short and long-term experiences with treatment provided by homeopaths to their experiences of antidepressant use, qualitative semi-structured audio-recorded interviews will be carried out with a purposive sample of patients (both genders, and different age groups, practitioners and degrees of depression) who are using or who have used antidepressants. Participants will be interviewed after their first consultation with a homeopath and after six months, focussing on patients' experiences with the first consultation and the HMP; and with their long-term experiences. A minimum of two researchers will check transcriptions and analysis of interviews. Thematic analysis will be used to allow for flexibility in the process of analysing data, during and after interviews. Interviews will be carried out until saturation, or when reaching the maximum number of 30 interviews. Reliability of results will be established by returning to and seeking confirmation of identified themes from current and former interviews, and by two persons assessing recordings. The validity of results will be established through the clarity and grounding in participants' responses.

Combining results from the quantitative and qualitative part of the study

A mixed methods approach including triangulation[31] will be used to combine results from the qualitative and quantitative methodologies at the interpretation stage. The aim of this will be to see if results obtained when using the two methodologies are convergent (agree), complementary (add complementary information) or contradict each other (discrepancy/dissonance).

Discussion

A significant number of depressed patients consult with practitioners of complementary and alternative medicine (CAM) and it is among the top ten complaints treated in homeopathy.[12,13,32] Studies report of 3.5% of homeopathy patients suffering from depression in the US,[32] 5.4% men and 6.0% women in Germany,[13] and mood disorders, including depression, are the most common complaints with 20.7% treated by UK homeopaths.[12]

Insufficient research evidence exists in order to draw any firm conclusions as to the acceptability and effectiveness of homeopathic treatment. Previous researchers have pointed out difficulties in applying double-blinded placebo-controlled randomised trial methodology in homeopathy, due to the individualised nature of homeopathic treatment.[33] These authors have pointed out that it may be that the specific and non-specific effects in homeopathic treatment affect each other. Others have offered theoretical models to explain an entanglement effect which might explain difficulties when using placebo controls.[34,35] There is a need for high quality clinical trials, and innovative methodologies are needed in order to address the individualised nature of this treatment, as well as challenges with recruitment and attrition. Informing patients that they may receive placebo does not occur in everyday practice and it affects their experiences, their behaviours and the results.[36,37] Moreover, research should provide evidence facilitating decision-making in

health care. These are some of the reasons why we propose to carry out a pragmatic RCT using the cohort multiple randomised controlled trial (cmRCT) design to test the acceptability and effectiveness of homeopathy in depression. The cmRCT is a novel design which has been and is currently being tested in psychiatric research.[38,39]

SYC participants have already given consent to be contacted again, to use their data to look at benefits of health treatments, and the majority have also given consent to look at their health records. Additional informed consent for homeopathic treatment will be sought from participants randomly selected to the Offer group and for qualitative interviews.

Baseline data on 'research ready' SYC participants is hoped to enable speedy identification of the study population and minimise the time spent on recruitment. In the cmRCT design patients are not told about treatments that they are not then offered, nor are they told that their treatment will be decided by chance. Providing information in this manner mimics the manner in which information is provided in routine healthcare and will help avoid resentful demoralisation as this is commonly experienced in standard open label pragmatic RCT designs. The study has obtained ethics approval from NRES Committee Yorkshire & The Humber (ref. 12/YH/0379).

Although patient reported outcome measures (PROMs) cannot replace properly carried out diagnostic interviews for identifying depression, PHQ-9 has been found to be a useful depression screening tool[28] and for a wide range of comorbidities.[28] Although weaknesses of PHQ-9 have been pointed out by some authors,[40] others found it has high degrees of reliability and validity in depression trials[28], with diagnostic validity comparable to clinician administered measures,[41] high sensitivity, specificity, and negative and positive predictive value,[42] and superior or equal to similar outcome measures[42]. It is sensitive to changes with treatment,[42] also in randomised controlled trials[43–45], and performs similarly whether self-reported by patients, completed using a computer, or administered by an interviewer over telephone.[28] It has been extensively used in routine psychology and psychotherapy practice.

Using triangulation to combine results from quantitative and qualitative methodologies will add to the understanding of the research question.

Declaration of interests

The authors declare that they have no competing interests.

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