Homeopathy for depression: a systematic review of the research evidence.

Karen Pilkington[1,2]
Graham Kirkwood[1]
Hagen Rampes[3]
Peter Fisher[4]
Janet Richardson[1,5]

[1] Research Council for Complementary Medicine, London, UK
[2] School of Integrated Health, University of Westminster, London, UK
[3] Barnet, Enfield & Haringey NHS Mental Health Trust, Middlesex, UK
[4] Royal London Homoeopathic Hospital, London, UK
[5] Faculty of Health & Social Work, University of Plymouth, UK

This is an electronic version of an article published in Homeopathy, 94 (3), pp. 153-163, July 2005. The definitive version in Homeopathy is available online at:

http://www.sciencedirect.com/science/journal/14754916

Homeopathy for depression: a systematic review of the research evidence

Karen Pilkington, Research Council for Complementary Medicine, London, UK[/]School of Integrated Health, University of Westminster, London, UK

Graham Kirkwood, Research Council for Complementary Medicine, London, UK

Hagen Rampes, Barnet, Enfield & Haringey Mental Health NHS Trust, Northwest Community Mental Health Team, Barnet, Enfield and Haringey Mental Health NHS Trust, Edgware, Middlesex, UK

Peter Fisher, The Royal London Homoeopathic Hospital, London, UK

Janet Richardson, Faculty of Health and Social Work, University of Plymouth, Devon, UK and Research Council for Complementary Medicine, London, UK[/]

Address for correspondence:

Karen Pilkington

Project Manager/Senior Research Fellow

School of Integrated Health

University of Westminster

115 New Cavendish Street

London W1W 6UW

United Kingdom

E-mail: k.pilkington@westminster.ac.uk

Tel no: 0207 911 5000 ext 3920

Short running title: Systematic review of homeopathy in depression

Keywords: homeopathy, depression, depressive disorder, systematic review

Abstract

Objective

To systematically review the research evidence on the effectiveness of homeopathy for the treatment of depression and depressive disorders

Methods

A comprehensive search of major biomedical databases including MEDLINE, EMBASE, ClNAHL, PsycINFO and the Cochrane Library was conducted. Specialist complementary and alternative medicine (CAM) databases including AMED, CISCOM and Hom-Inform were also searched. Additionally, efforts were made to identify unpublished and ongoing research using relevant sources and experts in the field. Relevant research was categorised by study type and appraised according to study design. Clinical commentaries were obtained for studies reporting clinical outcomes.

Results

Only two randomised controlled trials (RCTs) were identified. One of these, a feasibility study, demonstrated problems with recruitment of patients in primary care. Several uncontrolled and observational studies have reported positive results including high levels of patient satisfaction but because of the lack of a control group, it is difficult to assess the extent to which any response is due to specific effects of homeopathy. Single case reports/studies were the most frequently encountered clinical study type. We also found surveys, but no relevant qualitative research studies were located.

Adverse effects reported appear limited to ‘remedy reactions’ (‘aggravations’) including temporary worsening of symptoms, symptom shifts and reappearance of old symptoms. These remedy reactions were generally transient but in one study, aggravation of symptoms caused withdrawal of the treatment in one patient.

Comment [P1]:

Conclusions

A comprehensive search for published and unpublished studies has demonstrated that the evidence for the effectiveness of homeopathy in depression is limited due to lack of clinical trials of high quality. Further research is required, and should include well-designed controlled studies with sufficient numbers of participants. Qualitative studies aimed at overcoming recruitment and other problems should precede further RCTs. Methodological options include the incorporation of preference arms or uncontrolled observational studies. The highly individualised nature of much homeopathic treatment and the specificity of response may require innovative methods of analysis of individual treatment response.

Keywords: homeopathy, depression, depressive disorder, systematic review

Introduction

Mental health problems such as anxiety, depression and insomnia are among the most common reasons for individuals to seek treatment with complementary therapies in the US.[1] This survey revealed that prevalence of the use of complementary and alternative medicine for the United States in 1997 was 42 per cent with chronic conditions, including depression and anxiety, comprising the conditions for which therapies were most frequently sought: 40.9% of adults with depression and 42.7% of adults with anxiety had used complementary therapies in the previous year.[1]

Several surveys have focussed on the use of complementary and alternative medicine by patients with psychiatric disorders. Davidson and colleagues conducted a study to determine the frequency of psychiatric disorders in patients receiving complementary medical care in the UK and the USA.[2] Psychiatric disorders were relatively frequent among these patients. 74% of the British patients and 60.6% of the American patients had a lifetime psychiatric diagnosis. Major depression (52% of UK patients and 33.3% of USA patients) and any anxiety disorders were the commonest lifetime diagnoses. 46% of the UK patients and 30.3% of the USA patients had a current psychiatric diagnosis. Six per cent of the total currently suffered from a major depression and 25.3% of the total met the criteria for at least one anxiety disorder. A high rate of use of complementary therapies in adults who met criteria for common psychiatric disorders was also reported by Unutzer and colleagues.[3] Respondents who met the criteria for major depression and panic disorder were particularly likely to report use. Finally, a recent, large, prospective

study of 3981 patients consulting classical homeopaths in Germany demonstrated a similar situation with depression among the 10 most frequent diagnoses encountered.[4]

Depression

Depression refers to a wide range of mental health problems characterised by the absence of a positive affect, low mood and a range of associated emotional, cognitive, physical and behavioural symptoms. Behavioural and physical symptoms typically include tearfulness, irritability, social withdrawal, reduced sleep, exacerbation of pre-existing pain and pain secondary to increased muscle tension and other causes, poor appetite, lack of libido, fatigue and diminished activity, although agitation is also common and marked anxiety frequent. Along with a loss of interest and enjoyment in everyday life, feelings of guilt, worthlessness and deserved punishment are common, as are lowered self-esteem, loss of confidence, feelings of helplessness, suicidal ideation and attempts at self-harm or suicide. Cognitive changes include poor concentration and reduced attention, pessimistic and recurrently negative thoughts about oneself, one's past and the future, mental slowing and rumination.

Depression is the most common mental disorder in community settings, and is a major cause of disability across the world. In 1990, it was the fourth commonest cause of loss of disability adjusted life years in the world, and by 2020, it is projected to become the second commonest cause.[5] The estimated point prevalence for major depression among 16 to 65 year olds in the UK is 21/1000. If the broader category of "mixed depression and anxiety" is included, this rises to 98/1000. Apart from the subjective suffering

experienced by people who are depressed, the impact on social and occupational functioning, physical health and mortality is substantial. The impact on physical health sets depression alongside all the major chronic and disabling physical illnesses such as diabetes, arthritis and hypertension.[6]

A range of therapeutic approaches are available, the most widely used, in developed countries, is antidepressant drugs.[7] However these are associated with a number of problems including poor compliance and toxicity in overdose (particularly with the older tricyclic drugs) while the more modern selective serotonin uptake reinhibitor (SSRI) drugs are associated with increased incidence of self harm in young people and of suicide [8,9]. Patients may turn to complementary therapies due to side effects of medication, time and effort associated with non-pharmacological therapies, lack of response or simply preference for the complementary approach.

Homeopathy

Homeopathy is among the most popular of CAM therapies and is widely used in western European countries including France, Germany, the Netherlands and the UK. It is also popular elsewhere in the world, notably the Indian subcontinent and Latin America and there has been rapid recent growth of usage in the USA[1]. Its perceived safety is an important factor motivating patients to use homeopathy.[10] The extensive use of homeopathy, together with interest in homeopathy as a treatment for depression [11,12,13] suggested that a review of the evidence for effectiveness in this condition would be valuable**.**

Aim and objectives

The aim of this study was to evaluate the evidence from a range of sources on the effectiveness (and safety and patient satisfaction) of homoeopathy for the treatment of depression.

Methods

Summary of search strategy

A comprehensive search for clinical research was carried out. Systematic searches were conducted on a range of databases, citations were sought from relevant reviews and several websites were also included in the search, including those of MIND and the Mental Health Foundation.

Databases searched

General:

ClNAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, EMBASE, MEDLINE (and PubMed), PsycINFO, TRIP (Turning Research Into Practice) database

Specialist CAM and condition based:

AMED, CISCOM, Cochrane Complementary Medicine Field Registry, Hom-Inform, Cochrane Depression, Anxiety and Neurosis (CCDAN) Review Group trial register.

Search terms

The basic search terms for homeopathy included:

Exp homeopathy or Exp homeopathic drugs or Homoeop* or Homeop*

Terms for depression included:

Exp depression or Exp depressive disorder(s) or Exp dysthymia or Exp dysthymic disorder(s) or Depress* or Dysthym* or Mood or Affective disorder(s)

Search strategies were adapted for each of the databases searched and the CCDAN register and Hom-Inform databases were searched by the information specialists responsible for these databases. Efforts were made to identify unpublished and ongoing research using relevant databases such as the National Research Register (UK) and Clinicaltrials.gov (US) together with experts in the field. Searches of databases (general and specialist) were initially conducted from inception up to October 2003 and then repeated in February 2004 and searches for unpublished studies carried out in May 2004.

Filtering

Relevant research was categorised by study type according to a flow-chart system developed for this project. The basic categories used are shown in Table 1. Animal research and basic lab-based research were not included in the categorisation process.

Selection criteria

Types of study

- Initially only controlled studies were selected (randomised and non-randomised). As very few were located, other studies such as uncontrolled and observational studies were also included. Attempts were also made to locate relevant qualitative studies.

- No language restrictions were imposed at the search and filtering stage and translations were obtained for any potentially relevant studies in languages other than English.

Types of participants

- Participants with a primary diagnosis of depression or a depressive disorder and those with depression as part of/a result of a physical illness

Interventions

- All forms of homeopathy including individualised and complex. (Homeopathic complexes are fixed combinations of several homeopathic medicine)

Outcome measures

- Depression rating scales and patient focused measures such as satisfaction where relevant.

Data collection and analysis

Data was extracted systematically using a specially designed data extraction form. Data extracted included details of selection criteria and procedure, the participants, the intervention and any comparison or control intervention, aspects of the methodology and outcome measures and results. Clinical trials were appraised using a standardised appraisal framework specifically developed for this project and based on criteria recommended in the Centre for Reviews and Dissemination Report Number 4 (2nd Edition), Undertaking Systematic Reviews of Research on Effectiveness.[14]

Evaluation criteria included method of randomisation, allocation concealment and level of blinding (if relevant), method of dealing with missing values, loss to follow-up/withdrawals, measures of compliance and outcomes measures reported. The full criteria are shown in the tables of studies.

Data extraction and appraisal were conducted independently by two researchers (KP, GK) for each study and any disagreements or discrepancies were resolved by discussion. Where consensus could not be obtained, a third reviewer (JR) was available for consultation.

Clinical commentaries

Clinicians with training and experience in psychiatry and homeopathy and clinical research in these area (HR, PF) commented on studies focusing on clinical relevance and

practical issues. Commentary frameworks were specifically developed for this project, these incorporate a number of closed and open questions with space for further comments. Summaries of these commentaries are provided in the tables of studies.

Main results

Types of study and numbers identified (Figure 1)

Systematic reviews:

- No systematic reviews specifically on the topic of homeopathy for depression were identified. One systematic review [15] included an RCT of patients with mixed anxiety and depression [16] (included under Controlled clinical trials)

Controlled clinical trials:

Depression as primary diagnosis

- 2 RCTs [16,17] were identified

Depression as secondary diagnosis/part of physical illness

- 1 RCT (depression associated with chronic fatigue syndrome) [18,19] was located

Other studies located:

- 4 UCT/case series [20,21,22,23,24]
- 1 observational survey-based study [25]
- 1 multivariate analysis [26]

- Over 50 single case reports/studies
- A number of surveys and patient outcome studies

No relevant qualitative research studies were located

Language of studies located

Only one study in a language other than English was located [16]. A translation was obtained.

The Evidence

Based on conventional measures of quality and accepted study types, i.e. adequately randomised and controlled studies of sufficient power, no relevant studies were located. Those that were located were of low methodological quality, had insufficient numbers of participants or were uncontrolled. However, all located studies are presented in the tables together with comments on their methodology and clinical relevance in an attempt to highlight the issues to be addressed in future research in this area.

Summary of each study

Only one published randomised controlled trial examining the use of homeopathy for depression was located. This trial [16] , conducted in France, has been described previously as an 'open randomised study' [27] comparing homeopathic treatment with diazepam in patients with mixed anxiety and depressive states. Positive results for an homeopathic complex, a standardised proprietary formula, were reported. In the criteria-based systematic review of Kleijnen and colleagues[15] the trial scored only 45 out of 100 for

methodological rigour, the cut off point for better studies was ≥55. The use of an anxiolytic drug as a control appears inappropriate in a trial in patients with depression and further appraisal of the study revealed a lack of information on many of the measures of trial quality; the method of randomisation, whether assessors were blinded, compliance and co-interventions. There were also problems in the diagnostic classification and inappropriate outcome measures were used. In subsequent meta-analyses and reviews, no further controlled trials specific to homeopathy and depression are cited. [28,29,30,31,32] Studies conducted by the Homoeopathic Medicine Research Group, as a report to the European Commission, also failed to uncover any new controlled trials. [33,34]

A randomised controlled trial of homeopathy for depression in primary care was, however, conducted in 1999 at an East London group practice in collaboration with the Royal London Homeopathic hospital.[17] The aim of this pilot study was to assess the feasibility of a general practice based trial comparing the effectiveness of individualised homeopathic treatment against fluoxetine (Prozac) and placebo. The methodology described is rigorous; randomised, double blind and double dummy. However, difficulties with recruitment resulted in only 11 participants being recruited to the study, 4 in the treatment group with only 5 patients completing the study (personal communication).

Davidson and colleagues reported homeopathic treatment of 12 patients with a range of diagnoses related to depression and anxiety disorders. [21] Full psychiatric diagnostic assessment together with a comprehensive homeopathic interview took place followed by

individualised prescribing of the homeopathic treatment. 7 (58%) of patients were reported to have responded to homeopathic treatment, on the basis of the Clinical Global Improvement (CGI) scale, including 2 of the 3 patients with major depression. Type and potency of the remedies, duration of treatment and co-interventions varied between patients, as did the initial diagnoses leading to difficulties in interpreting the results. However, this study was considered relevant to practice and valuable as a preliminary report by a clinical commentator involved in the current review.

There are several studies of the effects of homeopathy on mood or depression scores (among other outcomes), in patients with conditions such as cancer and chronic fatigue syndrome.

A 1 year randomised controlled trial of the treatment of 64 patients with post viral fatigue syndrome or ME (myalgic encephalomyelitis), included self-assessed mood disturbance as an outcome measure and found greater improvement in the syndrome overall with patients treated with individualised homeopathy compared with those in the placebo group. [18,19] However, no other measures of mood or depression were taken and the significance of these results for patients with other conditions is unclear. For this reason, further details of this study are not included in the table of studies.

The studies in cancer patients are all uncontrolled and involve the use of homeopathy to treat a range of problems. Depression was only one of the problems reported and measured. These studies provide only relatively weak evidence of effectiveness, as lack

of a control group and reporting of a range of outcomes leads to difficulties in interpretation of the results, particularly when assessing the extent to which any response is due to treatment with homeopathy. However, the findings are relevant to practice and therefore will be described here.

Clover and colleagues reported a series of 50 cancer patients in whom response to homeopathy treatment had been assessed using the Hospital Anxiety and Depression Scale (HADS) and Rotterdam Symptom Checklist. [20] Improvements were seen on the psychological distress subscale of the latter when comparing scores on initial and later (3^{rd} and 4^{th}) visits and the percentage with normal HADS anxiety scores increased from 48% to 75% over this period However, the lack a control group, variable co-interventions and loss to follow-up of 58% lead to difficulties in interpretation of these findings.

More recently, in a well-designed uncontrolled clinical trial of the use of individualised homeopathy for symptom relief in 100 cancer patients, 52% of patients were found to have some improvement in depression scores at the end of the study period. [23] Up to 3 symptoms perceived by the patient as problematic were rated on a self-rating scale. Mood disturbance was assessed using the Hospital Anxiety and Depression Scale (HADS). At the beginning of the study, 37 patients were depressed with 20 having a diagnosis of depression (scores above 10) and 17 borderline depression (scores 8-10). There was a significant improvement in the mean depression score for the whole study group, comparing the baseline score with either the average over all visits or just the last visit ($p<0.05$). Overall, 52% of patients were found to have some improvement in depression

scores at the end of the study period (4-6 consultations later), with a mean improvement of 1.4 (95% CI 0.1-2.6). Attrition rate was high; only 52% completed the study and 17 patients suffered an aggravation of symptoms or return of old symptoms considered to be previously described remedy reactions. No adverse reactions resulted in withdrawal of treatment. Satisfaction with treatment was measured by self-completion questionnaire and was high amongst those who completed the study; 75% regarded homeopathic treatment as having been helpful or better.

In a further uncontrolled clinical trial of individualised homeopathy for symptoms of oestrogen withdrawal in 45 breast cancer patients, a significant improvement in depression score was found among women with depression, but not of the group overall. [24] Twenty-six of the patients had also been included in the 2002 study. [23] 89% of patients completed this study and again satisfaction with treatment was high; 67% regarded homeopathic treatment as having been helpful, very helpful or extremely helpful for their symptoms.

An observational survey-based study of homeopathic treatment in 269 women with gynaecological disorders, 38% of whom were assessed as having mood disorders has been reported .[25] However, no information is given on diagnosis, the information was extracted from standardised questionnaires completed by 31 gynaecologists and the 269 questionnaires returned represented a response rate of only 28.5%. Response to treatment was based on physician and patient assessment rated on a 5-point scale and for 67% of

women in the study (calculated on an intention-to-treat basis) a ‘very good’ or ‘good’ improvement in their mood disorder symptoms was recorded.

Finally, outcome studies including those of Clover [35], Richardson [36] and van Wassenhoven and Ives [13] have reported positive results in patients with a range of conditions including depression.

In summary, only two randomised controlled trials were identified. One of these, a feasibility study, is published in this issue of Homeopathy. It demonstrated problems with recruitment of patients in primary care. Several uncontrolled and observational studies have reported positive results including high levels of patient satisfaction. Because of the lack of a control group, it is not possible to assess the extent to which any response is due solely to the homeopathy. The interventions also varied including various types of homeopathy: individualised prescribing, ‘limited list’ prescribing and standardised complexes, further complicating interpretation of the findings.

Adverse effects reported in the studies located appear limited to ‘aggravations’ including temporary worsening of symptoms, appearance of new symptoms and reappearance of old symptoms. These reactions were generally transient but in one study, aggravation of symptoms caused withdrawal of the treatment in one patient.

Conclusions

A comprehensive search for published and unpublished studies has demonstrated that the evidence for the effectiveness of homeopathy in depression is limited due to a lack of clinical trials of high quality. When attempted, RCTs of good design have encountered problems, particularly with recruitment. Similar problems have been encountered in other RCTs in depression. The adverse effects reported in the studies were congruent with literature on the safety of homeopathy suggesting that homeopathic medicines may provoke adverse effects but these are relatively rare, mild and transient, although there is probably under-reporting.[37,38] A recent systematic review of the frequency of homeopathic aggravations in the placebo and verum groups of double-blind, randomised clinical trials did not identify clear evidence of the existence of homeopathic aggravations[39] contrary to the findings of audits in practice [40]. The situation with regard to safety can be summed up as follows:

> "*Homeopathic medications in high dilutions prescribed by trained professionals are probably safe and unlikely to provoke severe adverse reactions. It is difficult to draw definite conclusions due to the low methodological quality of reports claiming possible adverse effects of homeopathic medicines"* [37]

Implications for the future

If shown to be effective, homeopathy might be a useful therapeutic option in depression; potential benefits over existing treatments include high patient acceptability, lack of adverse effects and safety in overdose. However the evidence base is currently weak. The main problem in RCTs of homeopathy for depression has been recruitment. In

principle it is possible to overcome this problem by using a very large recruitment base. However, this would be inefficient and the low recruitment ratio such a design implies means that the recruited subjects would likely be atypical.

Further research is required, and should include well-designed controlled studies with sufficient numbers of participants. However, before launching such studies, development of methodologies and strategies to overcome recruitment problems is necessary. Patient preference, and the attitudes of health professionals appear to be important constraints to recruitment. Qualitative studies aimed at identifying and understanding patients' and health professionals' perceptions and attitudes should precede further RCTs. Methodological options include the incorporation of preference arms or uncontrolled observational studies although both are less rigorous than RCTs.[41], when well-designed, such studies give results similar to those of randomised controlled studies.[42] The highly individualised nature of much homeopathic treatment and the claimed specificity of response justifies innovative methods of analysis of individual response to treatment. For instance in 'participant-centred analysis', subjects are declared benefited, non-responder or harmed, on the basis of a predefined decision rule. Variables associated with these responses can then be analysed.[43]

Finally, a substantial number of case studies were located. These provide an indication of the range of remedies employed in patients whose symptoms include depression. However, conclusions about the effectiveness of homeopathic treatment cannot be drawn from these because of factors such as preferential reporting of successful or unusual cases, and regression to the mean. Such reports however might provide useful qualitative data concerning homeopathic treatment strategies, but synthesis of information from

individual case reports is complex and impeded by a lack of structure and absent information in many reports. Efforts to encourage the publishing of high-quality structured case reports [44] , or consecutive case series of may help to address these problems. Methods aimed at utilising or synthesising data held with individual case studies either as a potential form of evidence or at least, as an illustration of how homeopathy is used in individuals with depression, may prove a valuable and rewarding approach in the future.

Summary of studies

See separate file

Acknowledgements

Anelia Boshnakova, Electronic Information Officer, RCCM for advice and support with search strategies and searches.

Veronica Tuffrey, Senior Lecturer, School of Integrated Health, University of Westminster for advice and comments on statistical issues.

The Project Advisory Group and Specialist Advisory Group (mental health) for the NHS Priorities Project for advice and support to the project.

The NHS Priorities Project is funded by the Department of Health. The views and opinions expressed are those of the authors and do not necessarily reflect those of the Department of Health.

References

1 Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998; 280(18): 1569-75.

2 Davidson J, Rampes H, Eisen M, Fisher P, Smith R, Malik M. Psychiatric disorders in primary care patients receiving complementary medical treatments. *Compr Psychiatry* 1998; 39(1):16-20.

3 Unutzer J, Klap R, Sturm R, et al. Mental disorders and the use of the alternative medicine: results from a national survey. *Am J Psychiatry* 2000; 157(11):1851-7.

4 Becker-Witt C, Lüdtkeb R., Weißhuhna TER., Willicha SN. Diagnoses and Treatment in Homeopathic Medical Practice. *Forsch Komplementärmed Klass Naturheilkd* 2004; 11: 98-103

5 World Bank. *World Development Report: Investing in Health Research Development*. Geneva: World Bank 1993.

6 Cassano, P, Fava, M. Depression and public health: an overview. *J Psychosom Res* 2002; 53(4):849-857.

7 Boyer WF, Feighner JP. The financial implications of starting treatment with a selective serotonin reuptake inhibitor or tricyclic antidepressant in drug-naive depressed patients. In *Health Economics of Depression* eds Jonsson and Rosenbaum. Chichester: J Wiley 1993

8 Martinez C, Rietbrock S, Ashby D et al. Antidepressant treatment and the risk of fatal and non-fatal self-harm in first episode depression. *BMJ* 2005;330:389-393

9 Fergusson D, Doucette S, Glass KG et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials *BMJ* 2005;330:396-399

10 Sharples F, Van Haselen R, Fisher P. NHS patients' perspective on complementary medicine. *Complement Ther Med* 2003;11(4):243-248.

11 Knaudt P, Connor K, Weisler R, Churchill L, Davidson J. Alternative therapy use by psychiatric outpatients. *J Nerv Ment Dis* 1999; 187(11):692-5.

12 Demling J, Neubauer S, Luderer H-J, Worthmuller. A survey on psychiatric patients' use of non-medical alternative practitioners: incidence, methods, estimation, and satisfaction. *Complement Ther Med* 2002; 10(4):193-201.

13 Van Wassenhoven M, Ives G. An observational study of patients receiving homeopathic treatment. *Homeopathy* 2004; 93:3-11.

14 CRD (NHS Centre for Reviews and Dissemination) Report Number 4 (2nd Edition), *Undertaking Systematic Reviews of Research on Effectiveness*. York: CRD 2001.

15 Kleijnen J, Knipschild P, ter Riet G. Clinical trials of homeopathy. BMJ 1991; 302:316-23.

16 Heulluy B. Random trial of L.72 with Diazepam 2 in cases of nervous depression. [Essai randomisé ouvert de L 72 (spécialité homéopathique) contre diazépam 2 dans les états anxiodépressifs]. Metz: Laboratoires Lehning. Unpublished study. 1985.

17 Katz T, Fisher P, Katz A, Davidson J, Feder G. The feasibility of a randomised, placebo-controlled clinical trial of homoeopathic treatment of depression in general practice. *Homeopathy* 2005;94:xx-xx

18 Awdry R. Homoeopathy and chronic fatigue – the search for proof. *Int J Alternat Complement Med* 1996: 19-21.

19 Awdry R. Homoeopathy may help ME. *Int J Alternat Complement Med* 1996: 12-16.

20 Clover A, Last P, Fisher P, Wright S, Boyle H. Complementary cancer therapy: a pilot study of patients, therapies and quality of life. *Complement Ther Med* 1995; 3(3):129-33.

21 Davidson JRT, Morrison RM , Shore J, Davison RT, Bedayn G. Homeopathic treatment of depression and anxiety. *Altern Ther Health Med* 1997 3(1):46-49.

22 Davidson J, Morisson RM, Shore J, Davidson RT, Bedayn G. Homeopathic treatment of anxiety and depression Traitement homeopathique de l'anxiete et de la depression. *Homeopath Europ* 1997; 5(6): 8-12.

23 Thompson EA, Reilly D. The homeopathic approach to symptom control in the cancer patient: a prospective observational study. *Palliat Med* 2002; 16(3):227-33.

24 Thompson EA, Reilly D. The homeopathic approach to the treatment of symptoms of oestrogen withdrawal in breast cancer patients. A prospective observational study. *Homeopathy* 2003; 92(3): 131-134.

25 Zenner S, Weiser M. Homeopathic treatment of gynecological disorders: results of a prospective study. *Biomed Ther* 1999; 17(1): 31-5

26 Davidson J, Woodbury M, Morrison R, Shore J, Bedayn G. Multivariate analysis of five homoeopathic medicines in a psychiatric population. *Br Homeop J* 1995; 84(4):195-202.

27 Stevinson C. Evidence for the efficacy of complementary therapies in depression. *Focus Alternat Complement Ther* 1999; 4(3):111-4.

28 Ernst E, Resch KL. Clinical trials of Homoeopathy: A reanalysis of a published review. *Forsch Komplementarmed* 1996; 3:85-90

29 Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges L, et al. Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997; 350:834-43.

30 Ernst E, Rand JI, Stevinson C. Complementary therapies for depression: an overview. *Arch Gen Psychiatry* 1998; 55(11):1026-32.

31 Linde K, Melchart D. Randomized controlled trials of individualized homeopathy: a state-of-the-art review. *J Altern Complement Med* 1998; 4(4):371-88.

32 Jorm A, Christensen H, Griffiths K, Rodgers B. Effectiveness of complementary and self help treatments for depression. *Med J Aust* 2002; 176(Suppl): S84-96.

33 Boissel J, Cucherat M, Haugh M, Gauthier E. *Critical literature review on the effectiveness of homoeopathy: overview of data from homoeopathic medicine trials*, Homoeopathic Medicine Research Group. Report to the European Commission. Brussels. 1996: 195-210.

34 Cucherat M, Haugh MC, Gooch M, Boissel JP. Evidence of clinical efficacy of homeopathy: a meta-analysis of clinical trials. *Eur J Clin Pharmacol* 2000; 56(1):27-33

35 Clover A. Patient benefit survey: Tunbridge Wells Homoeopathic Hospital. *Br Homeopath J* 2000; 89:68-72.

36 Richardson WR. Patient benefit survey: Liverpool Regional Department of Homoeopathic Medicine. *Br Homeopath J* 2001; 90:158-62.

37 Dantas F, Rampes H. Do homeopathic medicines provoke adverse effects? *Br Homeopath J* 2000; 89:S35–38. [Full text available at www.rlhh.org.uk/conference (Proceedings 2)],

38 Fisher P, Dantas F, Rampes, H, The safety of homeopathic products. *J R Soc Med* 2002 95: 474-5.

39 Grabia S, Ernst E. Homeopathic aggravations: a systematic review of randomised, placebo-controlled clinical trials. *Homeopathy* 2003;92:92-8.

40 Thompson E, Barron S, Spence D. A preliminary audit investigating remedy reactions including adverse events in routine homeopathic practice. *Homeopathy* 2004;93:203-209

41 Silverman WA, Altman DG. Patient's preferences and randomised trials. *Lancet* 1996; 347: 171-4.

42 Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *New Engl J Med* 2000; 342: 1887-92.

43 Aickin M. Participant-centered analysis in complementary and alternative medicine comparative trials. *J Altern Complement Med* 2003; 9: 949-57.

44 Thompson T, Owen D, Swayne J. Editorial: The case for cases: publishing high-quality case reports in homeopathy. *Homeopathy* 2002; 91(1): 1-2.

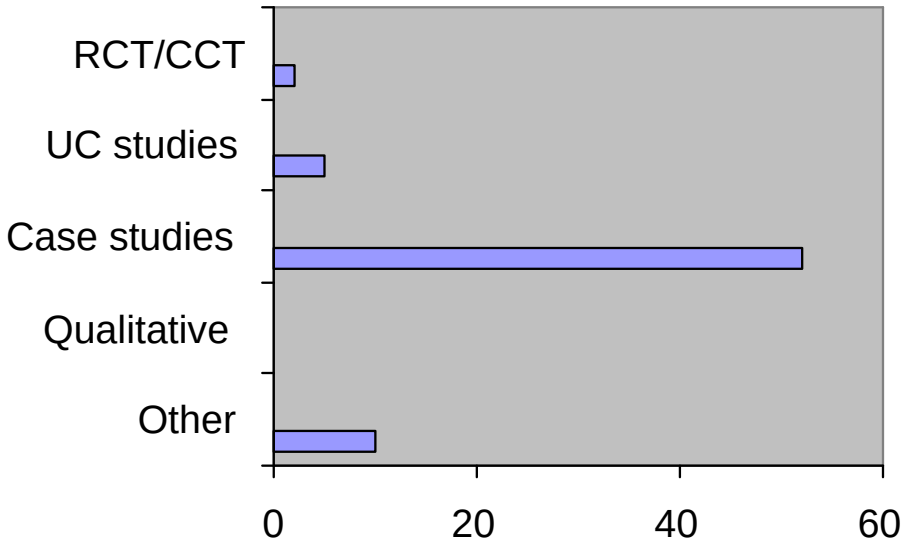

Figure 1 - Types of studies and numbers identified

Table 1 – Categories of study types used

RCT	randomised controlled trials
CCT	controlled clinical trials (without randomisation)
UC studies	uncontrolled studies including uncontrolled clinical trials and case series (further categorised according to the study population i.e. random sample, consecutive series or 'best' series)
Case reports/studies	reports of individual cases/patients
Qualitative research	study designs with a qualitative approach (including in-depth interviews and focus groups)
Surveys	large scale, primarily quantitative structured approaches
Other	research studies not falling into above categories

Summary of studies

Depression as primary diagnosis

Study	Study design	Sample	Inclusion criteria	CAM Rx	Control Rx	Outcome measure(s)	Results	Methodology comments	Clinical comments
Heulluy 1985	RCT (non-blinded)	N= 60 Tx= 30 Ct= 30 Setting and recruitment unknown	'Currently under consultation for depression, postmenopausal involution or thymo-effective dystonia'	Non – individualised L72 (constituents not specified) (twenty drops 4 times daily for 31 days) dose increased if required	Diazepam (dose and frequency unknown)	Ratio of pre and post scores for selected items on HAMD scale	L72 as effective as diazepam on all measures (thymo-effective, somatic and objective parameters) Negative outcomes: drowsiness (1 case for L72, 2 for diazepam)	Unknown method of randomisation, concealment of allocation, whether blinded (not attempted?), loss to follow-up/withdrawals, co-interventions, compliance	Intervention appropriate - Yes Control/placebo Appropriate - No/unclear Outcomes appropriate - No Diagnostic classification a problem
Katz et al (unpublished)	RCT pilot (triple arm parallel group) double-blind, double-dummy	N= 11 Tx(H)= 4 Ct(F)= 4 Ct(Pl) = 3 GP practice, East London. Recruited by GP homeopath	Major depressive episodes of moderate severity, duration 4+ wks, HAMD score 17+.	Limited list of 30 remedies, trained homeopath using decision support software. Remedy unchanged, dilution and regime adjusted Duration: 12 weeks	Fluoxetine 20mg daily increased to 40mg after 4 wks if no improvement in HAMD score and no adverse effects Placebo (matched tablets or capsules)	Primary: HAMD, CGI Secondary: SF12, QoL quest., WSDS, Pittsburgh Sleep Quality Index quest. Treatment credibility Side Effects checklist	Not reported due to low numbers	Planned methodology rigorous except for compliance (self-reported) and co-interventions (unknown). However recruitment was problematic (11 recruited) and loss to follow-up/withdrawals (6 completed)	Not sent for clinical commentary

Homeopathy in depression table of studies

Study	Study design	Sample	Inclusion criteria	Homeopathy Rx	Control Rx	Outcome measure(s)	Results	Methodology comments	Clinical comments
Davidson et al 1997	UC study (best case series?)	N= 12 (3 with depression) US hospital or homeopathic hospital. Recruitment process unclear	Social phobia, panic disorder, residual attention-deficit hyperactivity disorder, major depression, chronic fatigue syndrome	Full psychiatric assessment and homeopathic interview then individualised prescribing Duration variable (7-80 weeks)	N/A	CGI plus self-rated SCL-90 in the hospital, BSPS in the medical practice. Measures taken at variable intervals	58% (7) recorded a 50% reduction on the CGI scale 50% (6) recorded a 50% reduction on the SCL-90 or BSPS scale Response in2 out of 3 patients with major depression Negative outcomes: none reported	Not randomised, controlled or blinded. Compliance unknown Co-interventions – Drug and dose reported not frequency	Intervention appropriate Yes Control/placebo N/A Outcomes appropriate Yes Very relevant, excellent preliminary report

Depression as secondary diagnosis

Study	Study design	Sample	Inclusion criteria	Homeopathy Rx	Control Rx	Outcome measure(s)	Results	Methodology comments	Clinical comments
Clover et al 1995	UC study (consecutive case series)	N= 50 Referral to UK homeopathic hospital	Cancer-related symptoms (including mood disturbance)	Individualised homeopathy	None	HADS Rotterdam Symptom Checklist (RSCL) Initial, 2nd, 3rd and 4th clinic attendances	Improvements on the psychological distress subscale of RSCL comparing initial scores with 3rd and 4th visits ($p< 0.005$ and <0.02). Improvement in HADS Anxiety	Not randomised or blinded Loss to follow-up/withdrawals: 58% (29) reasons documented (15 died, 0 lost to follow-up) Co-interventions and other confounders: 29 (58%) prescribed SC	Intervention appropriate Yes Control/placebo N/A Outcomes appropriate Yes (for quality of life)

							subscale initial vs 3rd visits scores (p<0.01). (Initial visit 48% patient with normal HADS anxiety scores, 75% at 4th visit)	or oral iscador, 50% relaxation, 14% acupuncture, 34% CAM elsewhere	Well-designed and pragmatic cohort study
Thompson and Reilly 2002	UC study (consecutive case series)	N= 100 Referral to UK homeopathic hospital cancer clinic	Cancer-related symptoms (including mood disturbance)	Sixty minute consultation and prescription of individualised remedy Duration – variable	N/A	Self-rating of symptoms on 11 point scale HADS EORTCQLQ-30 At initial consultation and 4-6 consultations later	Initially 59 with anxiety, 37 with depression. For patients with at least 2 follow-ups mean anxiety scores improved by 1.6 (95%CI 0.4-2.9), mean depression scores by 1.4 (0.1-2.6) Negative: 17 patients with aggravation/return of old symptoms	Not randomised or blinded Loss to follow-up/withdrawals: 44% 56 completed (26 died, 18 defaulted) Co-interventions and other confounders: unknown	Intervention appropriate Yes Control/placebo N/A Outcomes appropriate Yes Excellent case series/cohort study
Thompson and Reilly 2003	UC study (consecutive case series)	N= 45 (26 from previous study) Outpatients at UK homeopathic hospital	Breast cancer patients with symptoms of oestrogen withdrawal (including mood disturbance)	60 minute consultation and Rx of individualised remedies (25 of variable potency, 30% as LM, for up to 3 symptoms). Pulsatilla,	N/A	Score of an effect on daily living of 3 symptoms (unvalidated) Scales were used at every consultation Symptom scores HADS	Significant improvement in all 3 main symptoms Mean anxiety scores improved by 2.1 (0.7-3.4) Mean depression scores improved by 1 (-0.1-2.1) not	Not randomised or blinded Loss to follow-up/withdrawals: 11% 40 completed (1 died, 4 defaulted) Co-interventions and other confounders: conventional cancer treatment, (55% tamoxifen, 48%	Intervention appropriate: Yes Control/placebo N/A Outcomes appropriate: Yes

				Sepia and Sulphur each given on more than 3 occasions as first Rx. Duration – variable		EORTCQLQ-30 (at initial consultation and 3-5 consultations later)	significant p=0.067 Negative : 7 with new symptoms, 10 with return of old symptoms. 1 withdrew due to aggravation of symptoms	adjuvant chemotherapy, 44% other medication including antidepressants)	Good study design but see Thompson et al 2002
Zenner and Weisner 1999	UC study (prospective, multicentre outcome based)	N= 269 Patients seen by one of 31 gynaecologists, Germany	Gynaecological disorders (including 102 with mood disorders)	Proprietary homeopathic remedy – Mulimen* given as drops (in 83% patients) or injection	N/A	Improvement in symptoms Patient and physician final evaluation on 5 point scale Tolerance on 4 point scale	Very good/good for between 75-80% cases for mood disorders (n=88) 77% recorded good/very good improvement in symptoms	Not randomised or controlled Loss to follow-up/withdrawals: results for 221/269 (82%) but response rate for questionnaire 28.5% Co-interventions and other confounders: 18% other medications, 2% other therapies	Intervention appropriate: Yes Control/placebo N/A Outcomes appropriate: Unsure

* constituents: Ambra grisca 4X, Calcium carbonicum Hahnemanni 8X,, Cimicifuga racemosa 4X, Gelsemium sempervirens 4X, Hypericum perforatum 3X, Kalium carbonicum 4X, Sepia officinalis 8X, Urtica urens 3X, Vitex agnus-castus 3X

Abbreviations: RCT randomised controlled trial, CCT controlled clinical trial, UC uncontrolled, DARE Database of Reviews of Effects, H homeopathy, D diazepam, HAMD Hamilton Depression Scale, P placebo, F fluoxetine, CGI Clinical Global Impression, QoL quality of life, WSDS Work and Social Disability Scale, BSPS Brief Social Phobia Scale, SCL-90 outpatient psychiatric rating scale, HADS Hospital Anxiety and Depression Scale, RSCL Rotterdam Symptom Checklist, EORTCQLQ-30 European Organisation for Research and Treatment in Cancer – Quality of Life Questionnaire – Core 30,

Research on patient satisfaction and experience with the therapy

- No qualitative studies were located
- The following studies addressed patient satisfaction and/or used patient outcome measures

Homeopathy in depression table of studies

Study	Study design	Results
Thompson 2002	Questionnaire (as part of study above)	75% of patients regarded homeopathic treatment as having been helpful or very helpful for their symptoms
Thompson 2003	Questionnaire	90% of patients rated their satisfaction as 7 or above on a 10 point scale (0=completely dissatisfied; 10=completely satisfied). 67% of patients regarded the homeopathic approach as helpful, very helpful or extremely helpful for their symptoms. 21% valued talking about the problem above the remedy, 36% valued both equally, 43% valued the remedy above talking