



ISSN Print: 2394-7500  
ISSN Online: 2394-5869  
Impact Factor: 5.2  
IJAR 2016; 2(6): 694-699  
www.allresearchjournal.com  
Received: 18-04-2016  
Accepted: 19-05-2016

**Dr. Sufal Halder**  
Senior Consultant Physician,  
Acharya Pranavananda  
Sevashram, Po: Purba  
Nischintapur, Budge Budge,  
Kolkata- 700138, India.

## Positive biofeedback of individualized homeopathic treatment and fluoxetine for moderate to severe depression in peri- and postmenopausal women

**Dr. Sufal Halder**

### Abstract

**Background:** The perimenopausal period refers to the interval when women's menstrual cycles become irregular and is characterized by an increased risk of depressive symptoms. Use of homeopathy to treat depression is widespread but there is a lack of clinical trials about its efficacy in depression in peri- and postmenopausal women. Previous trials suggest that individualized homeopathic treatments improve depression. In classical homeopathy, an individually selected homeopathic remedy is prescribed after getting a complete case history of the patient. The aim of this study is to assess the efficacy and safety of the homeopathic individualized treatment versus administration of placebo or fluoxetine in peri- and postmenopausal women with moderate to severe depression.

**Methods/design:** A randomized, placebo-controlled, double-blind and three-arm trial with a six-week follow-up study was designed. The statistical study was conducted in a public research hospital in Mexico City (Juárez de México Hospital) in the outpatient service of homeopathy. One hundred eighty nine peri- and postmenopausal women diagnosed with major depression according to the Diagnostic and Statistical Manual of Mental Disorders. The primary outcome is change in the mean total score among groups on the 17-item Hamilton Rating Scale for Depression after the fourth and sixth week of treatment. Secondary outcomes are: Beck Depression Inventory change in mean score, Greene's Scale change in mean score, response and remission rates and safety. Efficacy data was analyzed in the intention-to-treat population. To determine differences in the primary and secondary outcomes among groups at baseline and weeks four and six, data was analyzed by analysis of variance for independent measures with the Bonferroni post-hoc test.

**Discussion:** This study is the first trial of classical homeopathy that would evaluate the efficacy of homeopathic individualized treatment using C-potencies versus administration of placebo or fluoxetine in peri- and postmenopausal women with moderate to severe depression. It is an attempt to deal with the obstacles of homeopathic research due to the need for individual prescriptions in one of the most common psychiatric diseases.

**Keywords:** Perimenopause, Postmenopause, Depression, Homeopathy, Fluoxetine, Hamilton Rating Scale for Depression, Beck Depression Inventory

### Introduction

Major depressive disorder (MDD) is the fourth most disabling medical condition worldwide and it is expected to be ranked second by the year 2020 [1, 2]. It is typically recurrent and often chronic [3, 4]. MDD is associated with high health care costs [5]. Women are approximately twice as likely to develop MDD as men [4, 6]. The perimenopausal period refers to the interval when women's menstrual cycles become irregular, which generally occurs above the age of 40. Transition to menopause has long been considered a period of increased risk for depressive symptoms, as was demonstrated in the Harvard Study of Moods and Cycles, a population-based prospective study that examined the association between lifetime history of major depression and the decline in ovarian function [6]. According to the Stages of Reproductive Aging Workshop (STRAW), transition to menopause is the period that precedes menopause and it is characterized by variations in cycle length (>7 days different from baseline or  $\geq 2$  skipped cycles and an interval of amenorrhea  $\geq 60$  days) [7]. The postmenopausal stage is the period that continues after 12 months or more of amenorrhea.

**Correspondence**  
**Dr. Sufal Halder**  
Senior Consultant Physician,  
Acharya Pranavananda  
Sevashram, Po: Purba  
Nischintapur, Budge Budge,  
Kolkata- 700138, India.

Depressive symptoms increase during the transition to menopause [8]. A significant inverse association of follicle stimulating hormone (FSH) with depressive symptoms provides strong corroborating evidence that the changing hormonal milieu contributes to dysphoric mood in this transition period [9]. With menopause, serum levels of FSH usually exceed 40 mU/ml although, given the variability of individual hormone levels, the determination of menopausal status is generally made by clinical history rather than laboratory parameters. Furthermore, other hormones also change their serum concentrations. The decline in estrogen levels that is associated with menopause results in a wide range of symptoms, which include vasomotor symptoms (hot flushes and night sweats) [10].

The Hamilton Rating Scale of Depression (HRSD) and the Beck Depression Inventory (BDI) are two well-known standardized scales to assess depression severity used in trials worldwide. The Greene Climacteric Scale (GS) is also a standardized scale used in the Mexican population. It is intended specifically to be a brief and standard measure of core climacteric symptoms or complaints to be used for comparative and replicative purposes across different types of studies whether they are medical, psychological, sociological or epidemiological in nature. Three separate sub-scales measure vasomotor symptoms, somatic symptoms, psychological symptoms, and an additional probe is related to sexual function. Psychological symptoms can be further subdivided to measure anxiety and depression [11, 12].

Meta-analyses of antidepressant medications have reported only modest benefits over placebo treatment and, when unpublished trial data are included, the benefit falls below accepted criteria for clinical significance [13, 14]. Specifically, a meta-analysis of clinical trial data submitted to the US Food and Drug Administration (FDA) revealed a mean drug-placebo difference in improvement scores of 1.8 points on the HRSD [15], whereas the National Institute for Clinical Excellence (NICE) used a drug-placebo difference of three points as a criterion for clinical significance when establishing guidelines for the treatment of depression in the UK. Antidepressants may be effective for severely depressed patients, but not for moderately depressed ones. Moreover, only about 50% of patients with MDD show a response (>50% reduction in baseline symptoms) and only about one in three attain remission (virtual absence of symptoms) within the first eight weeks of treatment [4, 16-18].

Homeopathy is one of the most frequently used and controversial systems of medicine. It is based on the 'principle of similars'; highly diluted preparations of substances that cause symptoms in healthy individuals are used to stimulate healing in patients who have similar symptoms when ill [19]. When a single homeopathic remedy is selected based on a patient's symptoms picture, it is called 'classical' homeopathy [20]. In classical homeopathy, the treatment consists of two main elements: the case history and the prescription of an individually selected homeopathic remedy. The purpose of the homeopathic case history is to ascertain the totality of signs and symptoms of each patient, enabling the selection of an individualized homeopathic medicine [21].

Homeopathic medicines are produced through sequential agitated dilutions in Decimal (D), Centesimal (C) or Quinquagintamillesimal (Q or LM) potencies [21]. C-potencies are prepared by diluting a drop of a parent substance in 99 drops of ethanol followed by agitation of the solution (1 C). This procedure is repeated in consecutive agitated dilutions (2

C, 3 C, 4 C, and so on). Generally, high potencies are prescribed for mental symptoms.

Use of homeopathy to treat psychiatric and menopausal problems is widespread, and the need for more high-quality controlled trials has been identified [22, 23]. Meta-analyses and systematic reviews have drawn mixed conclusions as to whether homeopathy is more effective than placebo in general medicine [20, 24-28]. The database on studies of homeopathy and placebo in psychiatry is very limited, but results do not preclude the possibility of some benefit. Homeopathy efficacy was found for fibromyalgia and chronic fatigue syndrome, for example [22].

Bordet *et al.* conducted a multi-national prospective non-comparative observational study of homeopathic treatments for hot flushes and suggest that further investigation is justified [29]. Jacobs *et al.* conducted a randomized, double-blind study versus placebo performed over one year with 83 women suffering from breast cancer; patients received either individualized homeopathic treatment or a homeopathic complex or a placebo. This study did not show any significant difference between the three patient groups relative to the severity and frequency of hot flushes although there was a trend in the 'individualized homeopathic treatment' group during the first three months of the study [30]. Although depression is one of the most common symptoms in peri- and postmenopause, there is no controlled study of the homeopathic use of individualized treatment in depressive disorders in women at this stage.

Recently, results from a randomized, controlled, double-blind trial indicated that individualized homeopathic Q-potencies were non-inferior to the antidepressant fluoxetine in a sample of patients with moderate to severe depression [21, 31]. Responder rates (defined as a decrease of at least 50% from baseline on the Montgomery and Asberg Depression Rating Scale) were higher (homeopathy 84.6%, fluoxetine 82.8%) than those usually found for antidepressants in clinical trials (43% to 75%) [21, 31]. However, the efficacy of the individualized homeopathic C-potencies for peri- and postmenopausal women with depression has not been investigated.

## Aims

The primary aim of the study is to assess the efficacy of individualized homeopathic treatment (IHT) versus fluoxetine and placebo, and also a comparative study with administration of fluoxetine versus placebo in peri- and postmenopausal women with moderate to severe depression scored by the 17-item HRSD.

Secondary aims are: (1) to assess the efficacy of IHT versus fluoxetine and placebo, and fluoxetine versus placebo using the BDI and GS's score; and (2) to determine the safety of IHT versus fluoxetine and placebo, and fluoxetine versus placebo in peri- and postmenopausal women with moderate to severe depression.

## Methods/design

### Study design

The study was a randomized, placebo-controlled, double-blind and three-arm parallel and dominance trial with a six-week study duration.

### Participant recruitment

The recruitment methods will include advertisements through the internet, local media and community groups, and liaisons with general practitioners, gynecologists, psychologists and

allied health professionals. Posters with information about the study protocol was posted at the study site; brochures was distributed among the hospital population.

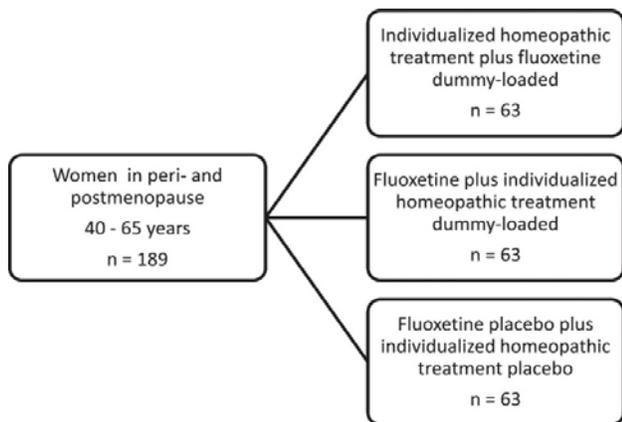
**Eligibility criteria**

The entry criteria for the study would be: (1) 40 to 65 years of age; (2) diagnosis of major depression according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV); (3) moderate to severe depression according to the 17-item HRSD (14 to 24 score); (4) no current use of homeopathic treatment for depression or antidepressants or anxiolytic drugs for three months prior to study entry; (5) not taking psychotherapy for at least three months before screening; (6) no use of estrogens or other medications known to affect ovarian function for at least three months before screening; (7) early transition to menopause, defined by a change in cycle length of seven days or longer in either direction from the participant’s own baseline for at least two cycles; or late transition to menopause, defined as three to eleven months of amenorrhea; (8) postmenopausal stage defined by 12 months or more of amenorrhea; and (9) capability and willingness to give informed consent and to comply with the study procedures.

Exclusion criteria include: (1) pregnancy or breastfeeding; (2) other psychiatric disorders different from moderate to severe depression (severe depression, schizophrenia, psychotic disorders, bipolar affective disorders, suicide attempt, and so on); (3) alcohol or other substance abuse; (4) known allergy to fluoxetine; and (5) cancer or hepatic diseases.

**Types of interventions**

After inclusion, patients was randomly assigned to either one of three groups illustrated in Figure 1: (1) IHT plus fluoxetine dummy-loaded; (2) fluoxetine (20 mg/day) plus IHT dummy-loaded; and (3) fluoxetine placebo plus IHT placebo.



**Fig 1:** Flow chart of the study groups

The selection of the individualized remedy would be carried out after taking the case history by a certified medical doctor, specialized in homeopathy with 18 years’ experience in classical homeopathy. The case history was based on Hahnemann’s methodology described in paragraphs 83 to 104 of Organon of Medicine, 6th edition. A complete medical history with clinical examination will also be done. All patients will have a full homeopathic case-taking including the collection of all the facts pertaining to the patient which may help in determining the totality of the symptomatology: past and present physical and emotional symptoms, family environment since childhood, stressful life events, marital

satisfaction. The symptoms was organized by hierarchy: mental, general and physical. In the first place, the strategy to choose the individualized remedy was based on the most characteristic and clear mental symptoms. Secondly, general symptoms was taken into account. A computerized version of the Synthesis Homeopathic Repertory 9.1 (Radar version 10) was used to facilitate the prescription. Only one remedy was prescribed at a time but it could be changed at every follow-up according to the patient’s symptoms.

Paying regards to this valuable study, C-potencies was provided by Hahnemann’s publishing Laboratory (Maxican

City) and were manufactured according to the Mexican Homeopathic Pharmacopoeia and Hahnemann’s methodology. Each individualized homeopathic remedy was prescribed in C-potencies. Higher initial potencies was tried, ranging from 30 to 200 C. The factors that influence the selection of the potency will include: clarity of mental symptoms, patient’s vitality and sensitivity, nature and kingdom (source) of medicine, chronicity and presence of any pathological disorder. A single dose of the individualized homeopathic remedy selected was dissolved in a 60 ml bottle of 30% alcohol-distilled water. Patients will receive 15 drops PO two times per day following agitation for 10 days, plus fluoxetine-dummy loaded prescribed PO daily. A double-dummy technique with matching placebos for each active treatment was applied, thus both placebos will seem identical to their corresponding *verum* formulations. Follow-up was at weeks four and six after the first clinical interview.

Patients in the fluoxetine group will receive 20 mg/day plus IHT-dummy loaded. IHT-dummy loaded was repeated at week four. Capsules of a generic fluoxetine was provided by Laboratorio Similia (Mexico City). Placebo capsules contain sucrose micro globules. Homeopathic placebo bottles was filled with the same amount of 30% alcohol-distilled water. Patients would receive 15 drops PO of this solution two times per day following agitation for 10 days. The homeopathic placebo was repeated at week four.

The third group will receive both fluoxetine and IHT placebos, as previously described.

**Criteria for discontinuing or modifying allocated interventions:**

Some adverse effects have been observed during fluoxetine treatment: lack of interest in sex, sexual dysfunction, nausea, insomnia, somnolence, anorexia, anxiety, asthenia, tremor, allergic skin reactions. If they are serious and/or result in interruption of treatment, they was reported as adverse events. During the IHT participants could have one of these reactions: (1) temporary intensification of symptoms before the condition improves, which is named ‘homeopathic aggravation’. If it occurs at all it is usually mild and simply an indication that the body is resolving the problem in a natural and healthy way. If aggravation is too distressing it was lessened by using frequent doses of the same remedy in a lower potency; (2) improving symptoms without aggravation; and (3) the appearance of new symptoms different from those on which the prescription was based. They was reported as adverse events. They are rarely serious, but in that case, the IHT was stopped. If the participant experiences the same symptoms of the remedy, the corresponding antidote was prescribed.

Each participant should receive a report form on which to write daily any adverse event observed during the trial duration.

### **Adherence to interventions**

To enhance the validity of the data, participants will return the unused capsules and bottles at each follow-up visit. Unused capsules was counted and recorded on the appropriate case report form. Participants was asked about any problems they are having taking their study treatment.

### **Concomitant interventions**

Some medications are prohibited during the study duration: triptans, tramadol, anxiolytic drugs, other serotonergic agents or antidepressants, as well as hormone replacement therapy. Psychotherapy is also forbidden during the study duration. Medication for diabetes and hypertension is allowed. The rescue intervention in case of a lack of efficacy in the IHT and placebo groups was fluoxetine 20 mg/day; in the fluoxetine group, the rescue medication was sertraline 25 mg/day.

### **Participant retention**

Plans to promote participant retention and complete follow-up would include: scheduling appointments and contacting patients by telephone.

### **Outcomes**

The primary efficacy outcome is the change from baseline in mean total depression score using the 17-item version of the HRSD at weeks four and six. The severity of symptoms was assessed by a blinded investigator (clinical psychologist) from the JMH. The secondary outcomes are: change from baseline in mean total depression score using BDI (a self-reported scale) at weeks four and six; change from baseline in mean total score of GS at weeks four and six; responder rates (response rate: decrease of 50% or more from baseline score; remission rate: HRSD  $\leq$ 7). The number and severity of all adverse events and homeopathic aggravations during the study period and 15 days after the final dose was collected to determine the safety of fluoxetine and homeopathic medicines. An adverse event was defined as any untoward medical occurrence in a subject without regard to the possibility of a causal relationship. Adverse events was collected after participants have given consent and enrolled in the study and 15 days after study completion.

### **Randomization**

Participants are simple randomized in a 1:1:1 ratio using a computer-generated random allocation sequence, by a statistician not further involved in the study. Participants would be assigned in sequential order to the treatment groups. The randomization list must be kept strictly confidential.

### **Allocation**

#### ***Concealment mechanism and implementation***

The principal investigator should enroll participants. Following inclusion, all patients should go through a full homeopathic case-taking and would receive a prescription of the individualized homeopathic medicine. Only one-third of the participants should actually receive a prescription. The research pharmacist must randomly deliver the treatment according to the allocation sequence in one of the three groups previously described. The randomization list must be sent to the research pharmacist at the start of the study. In case of emergency interventions, clinical worsening or adverse events, the pharmacist must inform the homeopathic doctor if the individual patient is taking homeopathy, fluoxetine or placebo, without disclosing the code.

### **Blinding**

Participants, the homeopathic doctor, the psychologist and the statistician must remain blinded to the identity of the three treatment groups until the end of the study. The psychologist assess the severity of the symptoms and keep the HRSD scores strictly confidential in a closed envelope at every follow-up until the end of the study.

### **Statistical analysis**

All patients under randomization would be included in the primary efficacy population (intention-to-treat population), regardless whether or not they adhered to the treatment protocol or provided complete data sets. Only patients who withdraw their consent to use their personal data would be excluded from the analysis. The flow of participants through the trial must be presented in a Consolidate Standards of Reporting Trials (CONSORT) diagram.

First, the three groups would be compared in order to verify that there are no significant differences among them at baseline to confirm they are comparable after randomization. Demographic characteristics would be summarized using means and standard deviation for continuous data (that is, age) and relative frequencies for qualitative data (that is, marital status, comorbidities). The baseline demographic characteristics among groups should be compared with the use of the chi square test or by one-way independent measures of variance (ANOVA) as required.

In this paper, it was compared: (1) IHT versus placebo; (2) fluoxetine versus placebo; and (3) IHT versus fluoxetine. The main statistical analysis would compare primary and secondary outcome measurements among groups at weeks four and six. The primary outcome (change in mean HRSD score) and secondary outcomes (change in mean BDI and GS scores) among groups at baseline and weeks four and six, would be analyzed by one-way ANOVA to provide a statistical test of whether or not the means of the three groups are all equal. The statistically significant one-way ANOVA result ( $P < 0.05$ ) suggests rejecting the global null hypothesis  $H_0$  (that the means are the same across IHT, fluoxetine and placebo groups). The Bonferroni *post-hoc* test would be used to determine which means differ among the groups. Responder rates would be compared among the groups using the chi square test. Statistical significance would be set at  $P < 0.05$  level for all analysis. Missing data must be handled by sensitivity analysis.

All patients who received at least one dose of the study drugs must be considered in the safety analysis. Adverse events was translated to Medical Dictionary for Regulatory Activities terms (MeDRA terms), quantified and compared among the groups using the chi square test. Homeopathic aggravation was compared among the groups also using the chi square test.

### **Discussion**

For the first time this study evaluates both the specific effect of IHT using C-potencies versus fluoxetine and placebo in peri- and postmenopausal women with moderate to severe depression. Besides comparing homeopathic medicines versus placebo, the fluoxetine-arm provides more useful information about the effect of IHT versus an efficacious treatment for depression in a randomized controlled trial. It is an attempt to deal with the obstacles of homeopathic research due to the need of individual prescriptions in one of the most common psychiatric disorders. Homeopathy is frequently prescribed for climacteric symptoms including depression as it has been

proven in some observational studies, but there is a lack of high-quality trials to prove its efficacy. This study protocol is based on: (1) CONSORT guidelines for reporting randomized trials with parallel groups; (2) the reporting data on homeopathic treatments (RedHot) supplement to CONSORT [32, 33]; and (3) the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidance for protocols of clinical trials [34].

It has been reported that the homeopathic consultation is in itself a therapeutic intervention working independently of the prescribed remedy [35], so all study participants must go through the same full homeopathic case-taking regardless of group allocation. Because placebo interventions are associated with mean response or remission rates of 35% [36, 37], this trial includes a placebo-arm, so placebo effect can be ruled out.

Gibbons *et al.* reported that patients in all age and antidepressant groups have significantly greater improvement relative to placebo controls; and fluoxetine has been proven to be efficacious for depression in adults after six weeks of treatment [38], so it is expected that the fluoxetine-arm should result in significant differences versus placebo in this study. However, Kirsch *et al.* reported that, at present, it is becoming more difficult to prove that antidepressants actually work better than placebo in moderate to severe depression. It also has to be taken into consideration that the antidepressant-placebo difference seems to be smaller in the trials with moderately depressed participants [13]. Therefore, a fluoxetine-arm should allow us to detect if in Mexican women in the climacteric stage with moderate to severe depression, the difference in HRSD score between fluoxetine and placebo is as small as it has been shown in some meta-analysis [13].

Otherwise, different scenarios can result if no significant differences between IHT and placebo groups are found. In classical homeopathy, recovery requires the prescription of the individualized remedy at the adequate potency and dosage, so this is an important factor to be taken into consideration during the trial process because results may be biased. A negative result could be due to a mistaken election of the remedy and not because the IHT is inefficacious. Follow-up duration is also important. The selection of a suitable, individualized homeopathic medicine would not always be accomplished during six weeks of treatment, especially under double-blind conditions [21]. It has not been proved that six weeks of IHT is enough time to find a clinically relevant response in climacteric women with depression. In routine homeopathic consultation, a patient may require more than six weeks to recover from depression. However, for ethical reasons a longer follow-up is not possible because of the placebo group. Furthermore, homeopathic prescriptions may need to be modified depending on a patient's individual response after homeopathic treatment is initiated. Once again, this could be problematic under double-blind conditions.

For ethical reasons women with severe depression was excluded, so data of this trial was able to prove an effective treatment in Mexican climacteric women with moderate to severe depression. Depression severity was scored by the 17-item HRSD, which is a standardized instrument that has been used in many other clinical trials for depression. Another self-administered instrument, the BDI may also be used, so the results of the study might provide useful information in clarifying the controversy over the efficacy of homeopathy in depression.

## Acknowledgement

In this paper, the author achieved extreme guidance favoring the in depth cultivation with a positive output from Dr. Partha Majumder, Biomedical Scientist, Human Physiologist and Systems Biologist, Former Principal Scientist (Helixinfosystems) and Former Head & Coordinator, Department of Applied Biotechnology and Bioinformatics, Sikkim Manipal University (CC:1637), Kolkata, India. Dr. Partha Majumder contributed a pioneer role to the design of the study, data analysis, and revision of the manuscript. It is an established fact that every mission needs a spirit of dedication and hard work but more than anything else it needs proper guidance. In fact, author feels proud in taking this opportunity to express his heartiest regards and deep sense of gratitude to his beloved Swami Mukteswaranaji Maharaj, President of Acharya Pranavananda Sevashram, located at Po: Purba Nischintapur, Budge Budge, Kolkata- 700138, India.

## References

- Greenberg PE, Stiglin LE, Finkelstein SN, Berndt ER. The economic burden of depression in 1990. *J Clin Psychiatry.* 1993; 54:405-418.
- Murray CJ, Lopez AD. Evidence-based health policy-lessons from the Global Burden of Disease Study. *Science.* 1996; 274:740-743. 10.1126/science.274.5288.740.
- Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR *et al.* National Comorbidity Survey Replication: The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA.* 2003; 289:3095-3105. 10.1001/jama.289.23.3095.
- Williams LM, Rush AJ, Koslow SH, Wisniewski SR, Cooper NJ, Nemeroff CB *et al.* International study to predict optimized treatment for depression (ISPOT-D), a randomized clinical trial: rationale and protocol. *Trials.* 2011; 12:4-10.1186/1745-6215-12-4.
- Simon GE, Von Korff M, Barlow W. Health care costs of primary care patients with recognized depression. *Arch Gen Psychiatry.* 1995; 52:850-10. 1001/archpsyc.1995.03950220060012.
- Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during menopausal transition. *Arch Gen Psychiatry.* 2006; 63:385-390. 10.1001/archpsyc.63.4.385.
- Hale GE, Zhao X, Hughes CL, Burger HG, Robertson DM, Fraser IS. Endocrine features of menstrual cycle in middle and late reproductive age and the menopausal transition classified according to the Staging of Reproductive Aging Workshop (STRAW) Staging System. *J Clin Endocrinol Metab.* 2007; 92:3060-3067. 10.1210/jc.2007-0066.
- Freeman EW, Sammel MD, Hui L, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry.* 2006; 63:375-382. 10.1001/archpsyc.63.4.375.
- Freeman EW, Sammel MD, Liu L, Garcia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry.* 2004; 61:62-70. 10.1001/archpsyc.61.1.62.
- Rapkin AJ. Vasomotor symptoms in menopause: physiologic condition and central nervous system

- approaches to treatment. *Am J Obstet Gynecol.* 2007; 196:97-106. 10.1016/j.ajog.2006.05.056.
11. Greene JG. Constructing a standard climacteric scale. *Maturitas.* 1998; 29:25-31. 10.1016/S0378-5122(98)00025-5.
  12. Hernández-Valencia M, Córdova-Pérez N, Basurto L, Saucedo R, Vargas C, Vargas A *et al.* Frequency of symptoms of the climacteric syndrome. *Ginecol Obstet Mex.* 2010; 78:232-237. Spanish
  13. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med.* 2008; 5:e45-10.1371/journal.pmed.0050045.
  14. National Institute for Clinical Excellence: Depression: Management of Depression in Primary and Secondary Care. *Clinical Practice Guideline.* London, 2004; 23:670.
  15. Kirsch I, Moore TJ, Scoboria A, Nicholls SS. The emperor's new drugs: an analysis of antidepressant medication data submitted to the US Food and Drug Administration. *Prev Treat.* 2002; 5:art 23-
  16. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am.* 1996; 19:179-200. 10.1016/S0193-953X(05)70283-5.
  17. Frank E, Prien R, Jarrett RB, Keller MB, Kupfer DJ, Lavon PW *et al.* Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse and recurrence. *Arch Gen Psychiatry.* 1991; 48:851-855. 10.1001/archpsyc.1991.01810330075011.
  18. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritzel *et al.* STAR\*D Study Team: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\*D: implications for clinical practice. *Am J Psychiatry.* 2006; 163:28-40. 10.1176/appi.ajp.163.1.28.
  19. Jonas W, Jacobs J. *Healing with Homeopathy.* 1996, New York: Warner
  20. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV *et al.* Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet.* 1997; 350:834-843. 10.1016/S0140-6736(97)02293-9.
  21. Adler UC, Krüger S, Teut M, Lütke R, Bartsch I, Schützler *et al.* Homeopathy for depression –DEPHOM: study protocol for randomized, partially double-blind, placebo controlled, four armed study. *Trials.* 2011; 12:43-10.1186/1745-6215-12-43.
  22. Davidson JR, Crawford C, Ives JA, Jonas WB. Homeopathic treatments in psychiatry: a systematic review of randomized placebo-controlled studies. *J Clin Psychiatry.* 2011; 72:795-805. 10.4088/JCP.10r06580
  23. Freeman MP, Mischoulon D, Tedeschini E, Goodness T, Cohen LS, Fava *et al.* Complementary and alternative medicine for major depressive disorder: a meta-analysis of patient characteristics, placebo-response rates, and treatment outcomes relative to standard antidepressants. *J Clin Psychiatry.* 2010; 71:682-688. 10.4088/JCP.10r05976blu.
  24. Onas WB, Kaptchuk YJ, Linde K. A critical overview of homeopathy. *Ann Intern Med.* 2003; 138:393-399. 10.7326/0003-4819-138-5-200303040-00009.
  25. Linde K, Melchart D. Randomized controlled trials of individualized homeopathy: a state-of-the-art review. *J Altern Complement Med.* 1998; 4:371-388. 10.1089/acm.1998.4.371.
  26. Ernst E. Homeopathy: what does the best evidence tell us?. *Med J Aust.* 2010; 192:458-460.
  27. Shang A, Huwiler-Müntener K, Nartey I, Jüni P, Dörig S, Sterne JA *et al.* Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet.* 2005; 366:726-732. 10.1016/S0140-6736(05)67177-2.
  28. Lüdke R, Rutten AL. The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials. *J Clin Epidemiol.* 2008; 61:1197-1204. 10.1016/j.jclinepi.2008.06.015.
  29. Bordet MF, Colas A, Marijnen P, Masson JL, Trichard M. Treating hot flushes in menopausal women with homeopathic treatment –results of an observational study. *Homeopathy.* 2008; 97:10-15. 10.1016/j.homp.2007.11.005.
  30. Jacobs J, Hermann P, Heron K, Olsen S, Vaughters L. Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary randomized controlled study. *J Altern Complement Med.* 2005; 11:21-27. 10.1089/acm.2005.11.21.
  31. Adler UC, Paiva NM, Cesar AT, Adler MS, Molina A, Padula AE *et al.* Homeopathic individualized Q-potencies versus fluoxetine for moderate to severe depression: double-blind, randomized non-inferiority trial. *Evid Based Complement Altern Med.* 2011, 520182-10.1093/ecam/nep114.
  32. Schulz KF, Altman DG, Moher D. CONSORT Group: CONSORT 2010 statement updated guidelines for reporting parallel group randomized trials. *PLoS Med.* 2010; 7:e1000251-10.1371/journal.pmed.1000251.
  33. Dean ME, Coulter MK, Fisher P, Jobst KA, Walach H. Reporting data on homeopathic treatments (RedHot): a supplement to CONSORT. *J Altern Complement Med.* 2007; 13:19-23. 10.1089/acm.2006.6352.
  34. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ.* 2013; 346:e7586-10.1136/bmj.e7586.
  35. Thompson TD, Weiss M. Homeopathy –what are the active ingredients? An exploratory study using the UK Medical Research Council's framework for the evaluation of complex interventions. *BMC Complement Altern Med.* 2006; 6:37-10.1186/1472-6882-6-37.
  36. Mulrow CD, Williams JW, Chiquette E, Aguilar C, Hitchcock-Noel P, Lee *et al.* Efficacy of newer medications for treating depression in primary care patients. *Am J Med.* 2000; 108:54-64. 10.1016/S0002-9343(99)00316-2.
  37. Dawson MY, Michalak EE, Anderson JE, Lam RW. Is remission of depressive symptoms in primary care a realistic goal? A meta-analysis. *BMC FamPract.* 2004; 5:19-10.1186/1471-2296-5-19.
  38. Gibbons RD, Hur K, Brown CH, Davis JM, Mann JJ. Who benefits from antidepressants? Synthesis of 6-week patient-level outcomes from double-blind placebo controlled randomized trials of fluoxetine and venlafaxine. *Arch Gen Psychiatry.* 2012; 69:572-579. 10.1001/archgenpsychiatry.2011.2044.