Alternative & Integrative Medicine
ISSN: 2327-5162

Klein-Laansma et al., Altern Integ Med 2014, 3:3
DOI: 10.4172/2327-5162.1000164

Research Article Open Access

Evaluation of Semi Standardized Individualized Homeopathic Treatment of 77 Women with Premenstrual Disorders: Observational Study with 9 Months Follow-Up

Klein-Laansma CT[1,2]*, Jansen JCH[1], Van Tilborgh AJW[1] and Van Vliet M[2]

[1]*Dutch Doctor's Association for Integrative Medicine (AVIG), The Netherlands*

[2]*Healthcare and Nutrition, Louis Bolk Institute, The Netherlands*

Abstract

Background: A large proportion (8-32%) of women in the fertile age suffers from premenstrual syndrome/ symptoms (PMS/S). Individualized homeopathy could offer relief and this should be further investigated. Semi-standardized treatment with a limited number of homeopathic medicines and strictly defined prescription criteria could minimize prescription variability and increase reproducibility of the individualized treatment.

Objective: In an extension of a previous pilot study, the utility of a semi-standardized algorithm with 11 medicines for individualized homeopathic treatment of women with PMS/S was further evaluated in daily practice with 9 months follow-up.

Methods: Women completed symptom diaries during to 2 months to confirm PMS/S. Women diagnosed with PMS/S were included, consulted a homeopathic physician and completed a questionnaire with keynote symptoms for 11 homeopathic medicines. A computerized algorithm would process the answers and indicate the first homeopathic prescription. At follow-up visits change of prescription was possible. Main outcome measures were frequencies and proportions of (non-) algorithm-based prescriptions during the study and percentage of responders (≥ 50% drop in PMS scores). Secondary outcome measures were mean changes in PMS scores over time.

Results: 77 women were included, 52 completed the study. The usefulness of the semi-standardized treatment protocol was confirmed. In 30 (57.5%) of the 52 analyzed women, PMS scores had dropped by ≥ 50%. For the estimated mean changes in PMS scores, it made no difference if women had used one or more of the 11 algorithm-based or also other homeopathic medicines (p=0.765). A significant association was found between symptom severity at baseline and changes in mean PMS scores (p<0.001).

Conclusions: A semi-standardized individualized homeopathic treatment of women with PMS/S with 11 medicines proved useful in daily homeopathic practice, with improved reproducibility of individualized treatment. This treatment could be further tested in effectiveness research.

Keywords: Premenstrual syndrome; Premenstrual symptoms; Homeopathy; Individualized; Personalized; Semi-standardized

Introduction

Premenstrual disorders

Worldwide, a meaningful proportion of fertile women (8-32%) suffer from moderate to severe physical and emotional symptoms during the luteal phase of the menstrual cycle [1]. The core premenstrual disorders are premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) [2]. Premenstrual symptoms can have an adverse impact on a woman's quality of life and lead to increased direct and indirect medical costs [3]. Moderate to severe PMS and PMDD are associated with impairment of work productivity and increased absenteeism and thus pose an economic burden [4].

Pharmacological treatments

Evidence-based pharmacological treatments for women with severe PMS or PMDD are antidepressants of the Selective Serotonin Re-uptake Inhibitor (SSRI) type and the Combined Oral Contraceptive (COC) drospirinone/-ethinylestradiol (Dros/EE) [5-7]. These treatments can effectively reduce symptoms, but have important limitations. The use of SSRIs would only be warranted for women with moderate to severe mental symptoms and not for women with mainly physical or mild mental symptoms. After discontinuation of treatment with SSRIs, relapse can occur so that long-term treatment would be required [8]. Many women suffering from PMS who were treated with SSRIs reported only minor improvements and no cure, implicating this treatment as 'effective but not enough' [9]. Also, women could object to taking antidepressants because of unwanted side effects or preference for a more 'natural and safe' treatment approach [5,10]. Women may be averse to treatment with COCs, because they want to get pregnant or have previously suffered from side effects of the drug. One of the leading researchers in the field concluded that the majority of women with PMS or PMDD would respond to any of the available treatments, but "further research to develop new therapies for the 40% of women with PMS who do not respond to the currently available treatments is needed" [11].

***Corresponding author:** Christien Klein-Laansma, Healthcare and Nutrition, Louis Bolk Institute, The Netherlands, Joubertweg 3, 6861 DM Oosterbeek, The Netherlands, Tel : +31 26 3341578 ; Fax: +31 26 4464549; E-mail: ctlaansma@planet.nl

Received May 08, 2014; **Accepted** July 14, 2014; **Published** July 16, 2014

Citation: Klein-Laansma CT, Jansen JCH, Van Tilborgh AJW, Van Vliet M (2014) Evaluation of Semi Standardized Individualized Homeopathic Treatment of 77 Women with Premenstrual Disorders: Observational Study with 9 Months Follow-Up. Altern Integ Med 3: 164. doi:10.4172/2327-5162.1000164

Homeopathic treatment of PMS

In an Israeli double-blind controlled pilot study, the effects of 5 specific homeopathic medicines were compared with placebo in 20 women with PMS [12]. The relative improvement rate of PMS symptoms in the verum group was significantly better than in the placebo group. In this study, a patient questionnaire containing questions representing so-called 'keynote' symptoms of 5 homeopathic medicines was used for the homeopathic medicine selection (keynote symptom: a specific symptom that strongly indicates the use of a particular homeopathic medicine). Women, whose symptoms did not match the profile of one of these 5 medicines, were allocated to a parallel trial. Other standardized as well as individualized homeopathic approaches have been explored in clinical studies of various design in the past [13-17]. Two more recent studies will be briefly discussed here. In a South-African double-blind placebo-controlled trial on individualized homeopathy in 39 women (27 completed the study), no statistical difference was detected between the placebo and verum group [18]. Homeopathic prescriptions were based on individual symptoms, but no details were revealed about a specific method of homeopathic medicine selection. A case series was published about individualized homeopathic treatment in 23 French women who reported premenstrual symptoms [19]. A positive impact on premenstrual symptoms and quality of life was observed in the majority of women.

The 'Dutch approach'

Inspired by the Israeli research, a semi-standardized homeopathic treatment of women with PMS was developed in the Netherlands. The aim of semi-standardization was to optimize the reproducibility of the treatment to facilitate clinical research and yet respect the individualized homeopathic treatment. The approach comprised a patient questionnaire to identify keynote symptoms for 11 selected homeopathic medicines and a computerized algorithm to process the answers. In 2007-2008 a pilot study was conducted to evaluate the feasibility of using the questionnaire and algorithm in 20 medical homeopathic practices in the Netherlands in 38 women suffering from premenstrual syndrome/premenstrual symptoms (PMS/S), with 3 months' follow-up [20]. The use of the questionnaire and algorithm was evaluated as feasible.

Rationale

Semi-standardized individualized homeopathic treatment could be beneficial for targeted subgroups of women with PMS. In an extension of a previous pilot study, the utility of an algorithm for homeopathic medicine selection was further evaluated with 77 women at 9 months' follow-up. The results of this evaluation, as discussed in this paper, will inform follow-up research.

Objectives

Primary objectives were to evaluate the use of the 11 selected homeopathic medicines, identify prognostic characteristics and calculate the overall proportion of responders. The main hypotheses were that at least 50% of the women in the study population could be treated by one of the 11 algorithm-based medicines, with satisfying results. Secondary objectives were to measure short- and long-term results by estimating changes of PMS scores over time and evaluate the association between use of the 11 selected homeopathic medicines and response to treatment. This extended observational pilot study was completed in mid-2011.

Methods

Design

A prospective uncontrolled observational study about individualized homeopathy with semi-standardized treatment was conducted in 20 homeopathic medical practices in the Netherlands.

Study size

The aim was to analyze data of 80 women. A sample size for this observational study was difficult to estimate, since no previous studies of similar design and follow-up duration have been carried out. In the preceding feasibility study, 38 of the 183 women who showed interest and received information were included. Based on these numbers, we would have to recruit 385 interested women.

Approval, recruitment, information and informed consent

The Medical Ethics committee (METc) of the Vrije Universiteit Medical Center (VUMC), Amsterdam, approved the study protocol. Women were recruited by articles and advertisements in newspapers and magazines, letters to general practitioners and by launching a website about the project. Women who were interested received written information with explanation about homeopathy in general, the Israeli pilot study and the outline of the present study. We informed that treatment costs would be reimbursed, if not covered by their own insurance company. Women were invited to contact a participating homeopathic doctor, plan an intake visit and provide informed consent. We kept no records of women who, after receiving information, did not make an appointment for an interview.

Inclusion and exclusion criteria and diagnosis

The inclusion criterion for the pre-treatment phase was a premenstrual symptom pattern as reported by women aged 18-50 years. Exclusion criteria were: a wish to get pregnant during the course of the study, use of antidepressants or hormones (except oral contraceptive pills (OCPs)), other treatment for PMS/S (except incidental use of painkillers or tranquillizers on single days) or recent homeopathic treatment for any disorder.

Before entering the treatment phase, volunteering women had to record their symptoms daily and prospectively on a 10-point scale during two months/cycles, to confirm the diagnosis PMS/premenstrual symptoms. The treating doctors confirmed or refuted the diagnosis and this was checked by the research coordinator. The 12 pre-defined premenstrual symptoms in the diaries are listed in Table 1. This diary was also used as a measurement instrument for calculation of PMS symptom scores (see below: Measurement instruments).

Pain or swelling of breasts
Headache
Joint- or muscle-pain
Swelling of hands or feet
Bloated abdomen
Feeling tense
Craving for food
Thirst
Irritability
Fatigue
Feeling down, depressed
Anxious feeling

Table 1: List of pre-defined symptoms in diaries.

ICPC-code	Diagnosis	Criteria
X89	Premenstrual syndrome	A cyclic occurrence in the menstrual cycle of two or more of the following symptoms during each of two consecutive cycles: peripheral oedema; breast tenderness/ swelling; headache; irritability; mood changes
X09	Premenstrual symptom/ complaint	A cyclic occurrence of at least one premenstrual symptom (as stated above) during two consecutive cycles, and the criteria for X89 are not met

Table 2: ICPC-2 criteria for PMS or premenstrual symptom/complaint.

Name	Abbreviation
Calcarea carbonica	*Calc-c*
Cimicifuga racemosa	Cimic
Lac caninum	Lac-c
Lachesis mutus	Lach
Lilium tigrinum	Lil-t
Magnesium carbonicum	Mag-c
Magnesium phosphoricum	Mag-p
Natrium muriaticum	Nat-m
Phoshorus	Phos
Pulsatilla pratensis	Puls
Sepia officinalis	Sep

Table 3: The 11 selected algorithm medicines in alphabetical order.

With a clear premenstrual pattern of at least one symptom and a symptom-free interval of at least 5 days in the follicular phase (=before ovulation), a woman could be included and enrolled into either the diagnosis category premenstrual syndrome or the category premenstrual symptoms. We used the International Classification of Primary Care (ICPC)-2 criteria for premenstrual syndrome (code: X89) and premenstrual symptom/complaint (code: X09). The criteria are summarized in Table 2.

Homeopathic treatment

The participating women were treated in in various regions in the Netherlands by 20 homeopathic doctors in their own practice, all members of the Dutch Association of Homeopathic Doctors (VHAN) and trained in classical homeopathy. All treating doctors had practical experience in homeopathy of more than 5 (most with more than 10) years. Before the first visit, participating women completed a homeopathic questionnaire with 123 questions, representing keynote symptoms for 11 homeopathic medicines. The answers were transferred to the computerized diagnostic algorithm, which would present a priority list for the 11 homeopathic medicines. The doctors consulted the algorithm, followed the instructions and prescribed the first homeopathic medicine as indicated by the algorithm. At follow-up visits (after 1, 2, 3, 5, 7 and 9 months/cycles), they could continue the first (algorithm-based) prescription, or prescribe another (algorithm-based or non-algorithm-based) medicine, according to their own professional opinion. The duration of the first consultation was approximately one hour and follow-up consultations would take half an hour on average. It was not dictated what potencies could be used, but the doctors were restricted to use potencies that were considered safe according to the European Directive 2001/83/EC [21]. The study medication was dispensed and sent by regular post by the Hahnemann Pharmacy, Heiloo, The Netherlands. If registered in the Netherlands, the medicines were manufactured by VSM, Alkmaar, The Netherlands. Unregistered medicines could be manufactured by the Hahnemann pharmacy or obtained from other manufacturers.

The medicines that were selected for the algorithm are listed in Table 3. The treating homeopathic doctors would inform the women as usual about how to take the homeopathic medicines, what changes could be expected, the possibility of aggravations, etc. Women who took conventional medicines for concomitant conditions before entering the pre-treatment phase, continued to do so during the study.

Measurement instruments

For two months before treatment and during the first three and final three months of the treatment, the women kept daily records about premenstrual symptoms, use of medication and absence from work.

Before every follow-up visit they completed a short questionnaire, with a Likert scale ranging -4 to +4 called AGOS (Adapted Glasgow Homeopathic Hospital Outcome Score), as previously described [22]. The AGOS for symptoms rated changes in premenstrual symptoms, while the AGOS for general health rated changes in general health, both compared to the start of the treatment.

Data collection

Data were collected between October 2007 and April 2011. A study outline is presented in Figure 1. At baseline the following characteristics were recorded: age, diagnosis (X89 or X09), duration of symptoms, age of menarche, co-diagnoses, and use of conventional medicines for PMS/S, contraceptive methods, number of pregnancies and of births, history of sexual abuse, post-partum depression (PPD) and other psychiatric illness. For each woman, the baseline premenstrual symptom score (PMS score) was calculated and recorded. It was based on the diaries and defined as the sum of daily scores of the second premenstrual period (14 days) in the pre-treatment phase. Baseline premenstrual symptom scores up to and including 150 were defined as 'mild' symptoms and scores above 150 as 'moderate to severe' symptoms.

During the treatment phase, calculations of the PMS scores, use of extra medication (to a maximum of 2 different medicines) and loss of work days were based on diary reports during 14 days prior to the start of menses. Intermediate outcomes of these parameters were assessed after 3 months, 7 months and ≥ 8 months (end scores), depending on the duration of treatment for the individual participant.

Prescription reports were collected at all consultations. The sequence of homeopathic prescription types (algorithm-based or non-algorithm-based) throughout the study was evaluated in retrospect at the 5th follow-up visit after 7 months, because at the 6th follow-up the study would be completed and if women wished to continue the homeopathic treatment, problems other than PMS would also be targeted. We invited all doctors to report adverse events or worsening of symptoms.

AGOS scores were recorded just before each follow-up visit. We collected all AGOS questionnaires and evaluated the AGOS scores at the 3rd and last follow-up consultation. The diaries and questionnaires were collected by the treating doctors and were sent to the research coordinator. The doctors reported the details of the homeopathic prescriptions at all consultations: name, potency, dose, frequency.

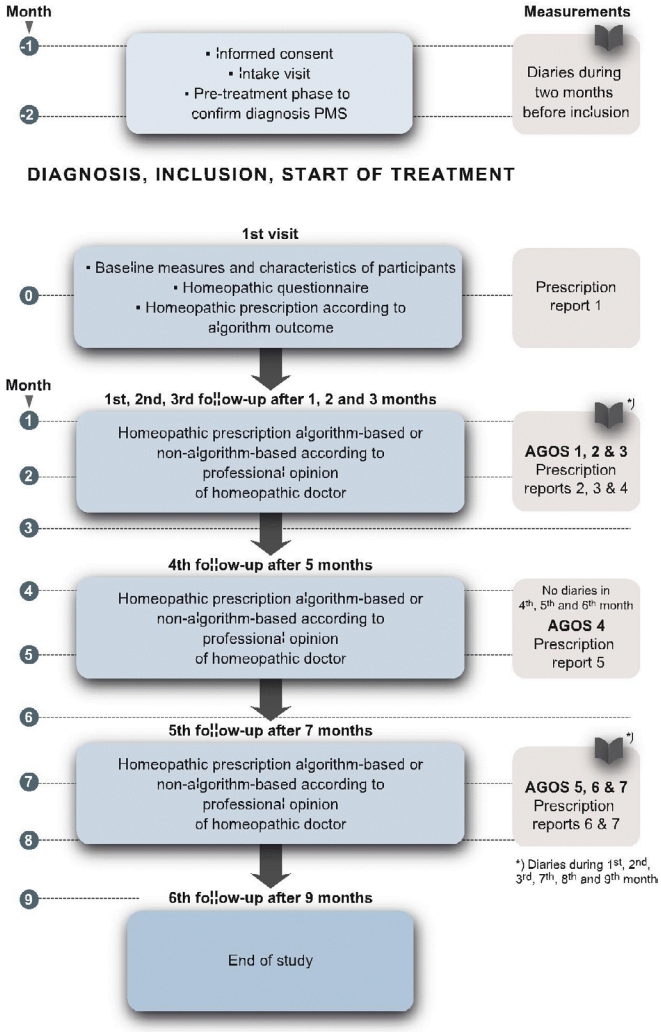

Figure 1: Study Outline.

Outcome measures

Primary outcome measures were:

1a) Frequencies of actual 'algorithm-based' or 'non-algorithm-based' medicine prescriptions as measured by cross-section at the 1st visit and at the 3rd and 5th follow-up. An algorithm-based medicine was defined as a prescription according to the algorithm outcome. A non-algorithm-based medicine was defined as any other homeopathic prescription.

1b) Sequence (change/continuation) of algorithm-based and non-algorithm-based medicine prescriptions in all participants since the first visit as assessed retrospectively at the 5th follow-up visit.

1c) Frequencies of identified women in two 'overall prescription categories': those who received 'only algorithm-based' medicines versus those who received 'also non-algorithm-based' homeopathic medicines throughout the study, as assessed retrospectively at the 5th follow-up.

2) Percentage of 'responders' defined as women with a clinically relevant improvement in PMS score. PMS scores were defined as the total sum of daily scores of 12 pre-defined symptoms in the 14 days prior to the start of menstruation. Response to treatment was defined as ≥ 50% reduction in symptom ratings (PMS scores). In the literature, this is considered a clinically relevant improvement in PMS/PMDD treatment trials, 'although smaller differences may also be meaningful' [23]. We measured intermediate response after 3 months (measured in the cycle preceding the 3rd follow-up), after 7 months (measured before the 5th follow-up) and the final response after 8 months or more (the first of two cycles recorded before the last follow-up visit).

3) Association between baseline characteristics (age, use of contraceptives, severity of symptoms, psychiatric history, chronic co-morbidity) and 'response' to treatment.

Secondary outcome measures were:

4) Changes in mean PMS scores measured at consecutive visits, adjusted for 'overall prescription category' ('only algorithm-based' medicines versus 'also non-algorithm-based' medicines) and symptom severity at baseline ('mild PMS symptoms' versus 'moderate to severe PMS symptoms').

5) Association between 'overall prescription category' and 'response' to treatment at the 5th follow-up visit.

6) Self-reported changes of symptoms and general health before the 3rd and last follow-up visit as measured by the AGOS.

7) Correlation between AGOS scores and PMS scores.

Analysis

Because of the observational nature of this evaluation study, per protocol analysis was applied for the primary and secondary outcome measures, unless otherwise stated (n=54). Incidental missing values were regarded as minor protocol violations and therefore 15 women who completed the study with incomplete intermediate reports were included in the analysis. Data were analyzed using SPSS 19.0. A two-sided p-value ≤ 0.05 was considered statistically significant.

Analysis of primary outcomes: 1. Descriptive statistics were used to: a) calculate frequencies of algorithm-based and non-algorithm-based medicine prescriptions, b) evaluate sequences of algorithm-based and non-algorithm-based prescriptions, c) calculate frequencies of women in the two 'overall prescription categories' as defined before.

2. Descriptive statistics were used to measure the proportion of responders.

3. Logistic regression was used to find possible associations between baseline characteristics (e.g. age, symptom severity, chronic co-morbidity, psychiatric history) and 'response' to treatment.

Analysis of secondary outcomes: 4. linear models were built by mixed models analysis. This method was chosen since it can deal with missing values. Mixed models analysis was used to determine the association between 'symptom severity' at baseline (mild or moderate to severe) as well as 'overall prescription category' (based on prescription reports after the 5th follow-up) and changes in PMS scores throughout the study.

5. Descriptive statistics were used to evaluate the association between the identified 'overall prescription category' and 'response' to treatment.

6. Descriptive statistics were also used to evaluate AGOS for symptoms and general health.

7. Spearman's correlation coefficient was used to calculate the correlation between the AGOS scores and PMS scores.

Results

Participants, dropouts and missing data

Recruitment took place between October 2007 and April 2010 and was paused between August 2008 and February 2009, for an intermediate evaluation of reimbursed treatment costs within the study budget. 77 women with premenstrual symptoms were found eligible and were included for the treatment phase. A flow chart is presented in Figure 2.

The age range was 24-49, the mean age 38.44 years. In 7 participants a major improvement of symptoms (drop of PMS scores of ≥ 50% between the first and second cycle) was observed during the pre-treatment phase. However, we did not exclude these women from further participation, considering this was an observational study. In Table 4, characteristics of women at baseline are presented, as well as associations between baseline characteristics and completers versus dropouts. The dropout rate was considerable. A relatively higher dropout rate was found in two categories: in women diagnosed with premenstrual symptoms (X09) compared to premenstrual syndrome (X89) (Chi-square test, two-sided, p=0.019) and in women with a psychiatric history (other than PPD) compared to women without a

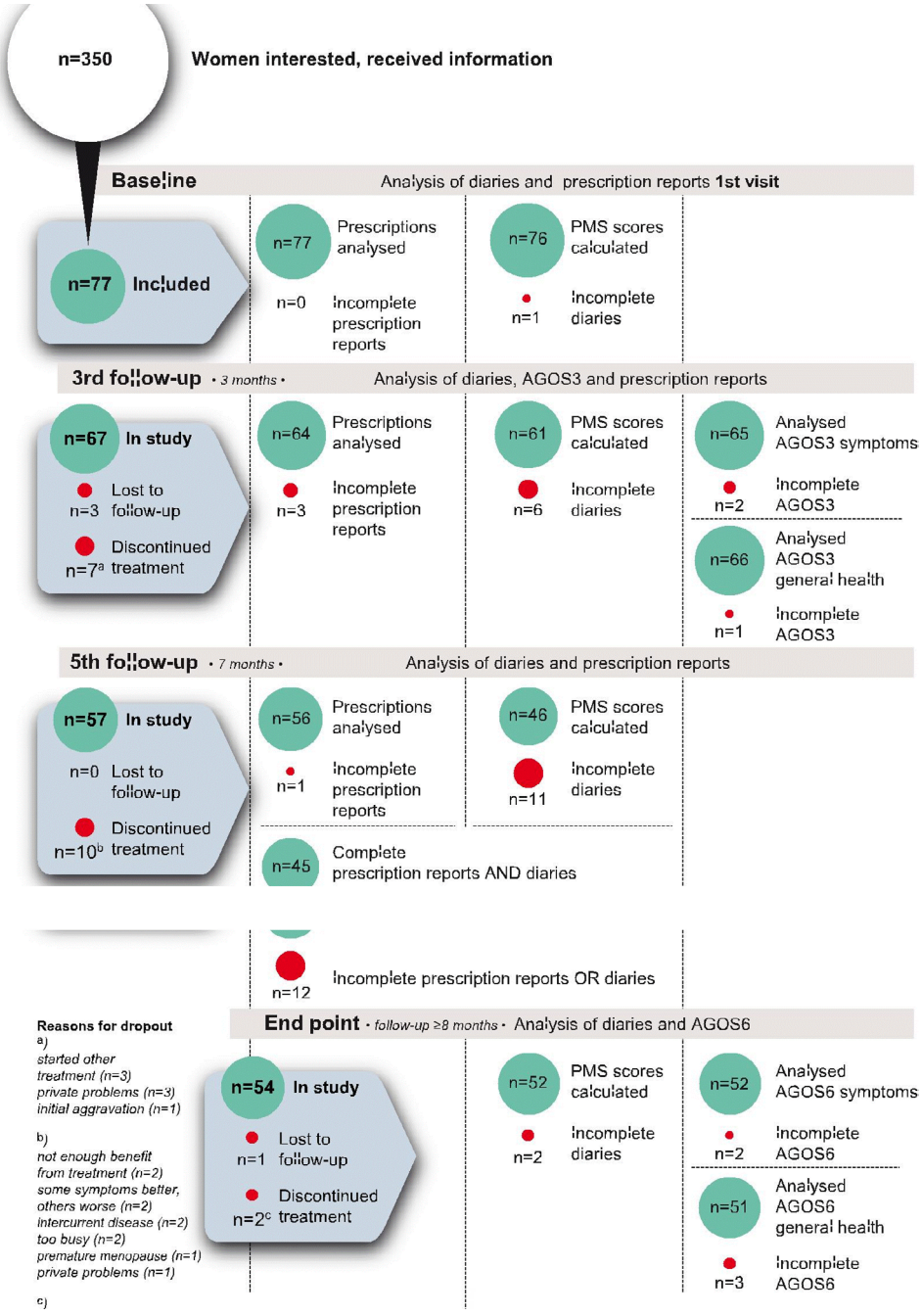

Figure 2: Flowchart.

Baseline characteristics	Total (N=77)	Completed study (N=54)	Dropouts (N=23)	Pearson 2-sided chi-square test
Age. 3 groups				*P=0.229*
18-30 years	7 (9.1%)	3 (5.6%)	4 (17.4%)	
31-40 years	41 (53.2%)	29 (53.7%)	12 (52.2%)	
41-51 years	29 (37.7%)	22 (40.7%)	7 (30.4%)	
Contraceptive methods	*(N=74)*	*(N=52)*	*(N=22)*	*P=0.790*
OCP	5 (6.7%)	4 (7.7%)	1(4.5%)	
Levonorgestrel-releasing IUD	3 (4.0%)	2 (3.8%)	1(4.5%)	
Copper IUD	4 (5.4%)	2 (3.8%)	2 (9.1%)	
None	62 (83.8%)	44 (84.6%)	18 (81.8%)	
Co-morbidity	*(N=77)*	*(N=54)*	*(N=23)*	
Yes	43 (55.8%)	30 (55.6%)	13 (56.5%)	*P= 0.938*
Diagnosis category	*(N=74)*)*	*(N=53)*	*(N=21)*	***P= 0.019***
PMS symptoms (X09)	9 (12.0%)	3 (5.7.%)	6 (28.6%)	
PMS syndrome (X89)	65 (88.0%)	50 (94.3%)	15 (71.4%)	
Psychiatric history	*(N=69)*	*(N=49)*	*(N=20)*	***P= 0.006***
Post partum depression (PPD)	9 (13.0%)	8 (16.3%)	1 (5.0%)	
Other psychiatric diagnosis	10 (14.5%	3 (6.1%)	7 (35.0%)	
No psychiatric diagnosis	50 (72.5%)	38 (77.6%)	12 (60.0%)	
PMS scores at baseline	*(N=76)*)*	*(N=53)*	*(N=23)*	*P= 0.721*
Mild symptoms	34 (44.2%)	23 (43.4%)	11 (47.8%)	
Moderate to severe symptoms	42 (55.3%)	30 (56.6%)	12 (52.2%)	
Overall prescription category (whole study)	*(N=67)*	*(N=54)*	*(N=13)*	*P= 0.455*
All according to algorithm	35 (52.2%)	27 (50.0%)	8 (61.5.4%)	
Not all according to algorithm	32 (58.2%)	27 (50.0%)	5 (38.5%)	

Table 4: Association between baseline characteristics and completers/dropouts as well as association between baseline characteristics and 'overall prescription category'.

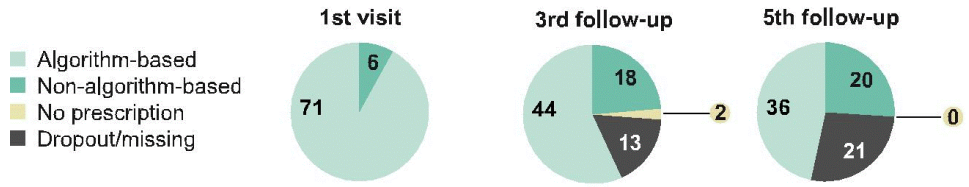

Figure 3: (Non)-algorithm-based prescriptions at the 1st visit, and at the 3rd and 5th follow-up.

psychiatric history (Chi-square test, two-sided, p=0.006).

Throughout the study, reports could be incomplete or missing. Numbers with complete reports could vary for diaries, AGOS questionnaires (both completed by patients), or prescription reports (completed by doctors). 39 women had complete reports and diaries at all measurement points. No influence of baseline characteristics on complete or incomplete data was found (Chi-square test, two-sided; age group: p=0.910; contraceptive method: p=0.897; co-morbidity: p=0.414; diagnosis category: p=0.072; psychiatric history: p=0.264; PMS scores at baseline: p=0.504).

Duration of follow-up

The timing of the 3rd follow-up visit varied from 2.5 to 4 months. The final visit took place after 8 or 9 months in 38 women, after 10 or 11 months in 11 women and after 12 months or more in 5 women. The mean duration of treatment was 7.5 months and the median was 8.0 months.

Primary outcomes

1a) The proportion of algorithm-based prescriptions declined considerably between the 1st visit and the 3rd follow up and then stabilized. At the first visit, 92.2% of the prescriptions was algorithm-based (n=71), this was 68.8% at the 3rd follow-up (n=44) and 64.3% at the 5th follow-up visit (n=36). Numbers of (non-) algorithm-based prescriptions and dropouts/missing values per visit are presented in Figure 3.

1b) In 17 of the 36 women who were using an algorithm-based medicine at the 5th follow-up, the prescription had been unchanged since the start of the study (47.2%).

1c) In total, 29 women had used only one or more algorithm-based medicines during the study (51.8%), while 27 had used also non-algorithm-based homeopathic medicines (48.2%) as measured in retrospect at the 5th follow-up.

2) At the end of the study, 57.7% (30 out of 52) of the women in the study were identified as responders (decrease of PMS scores ≥ 50%). In table 5, details are given about the percentage of responders and other result categories throughout the study.

3) In the responders group, no characteristics were found that were independently associated with a 50% drop in PMS scores.

	3rd follow-up		End visit	
Result category	N	*Valid %*	N	*Valid %*
Positive response	25	*41.7*	30	*57.7*
Moderate improvement	10	*16.7*	8	*15.4*
No change/unsure	15	*25.0*	8	*15.4*
Deterioration	10	*13.0*	6	*11.5*
Analyzed	60	*100*	52	*100*
Dropouts, missing/incomplete reports	17		25	
Total	77		77	

Table 5: Numbers and percentages of women in various result categories.

AGOS scores	3rd follow-up visit				End visit			
	Changes in premenstrual symptoms		Changes in general health		Changes in premenstrual symptoms		Changes in general health	
Score	N	%	N	%	N	%	N	%
+4	1	1.5	1	1.5	2	3.8	2	3.8
+3	13	20.0	4	6.1	18	34.6	10	18.9
+2	16	24.6	11	16.7	8	15.4	7	13.2
+1	14	21.5	13	19.7	16	30.8	11	20.8
0	12	18.5	26	39.4	2	5.8	17	34.0
-1	3	4.6	7	10.6	3	5.8	1	1.9
-2	2	3.1	2	3.0	2	3.8	3	3.9
-3	4	6.2	2	3.0	0	0	1	1.9
-4	0	0	0	0	0	0	0	0
Evaluated	65	100	66	100	51	100	52	100
Invalid/ missing score/ dropout	12		11		26		25	
Total	77		77		77		77	

Table 6: AGOS scores for symptoms and general health.

Secondary outcomes

4) No significant association was found between 'overall prescription category' ('only algorithm-based' versus 'also non-algorithm-based') and changes in mean PMS scores throughout the study (n=54; p=0.765). Meanwhile, an overall effect was detected: a significant association was found between symptom severity at baseline (mild or moderate to severe) and changes in mean PMS score throughout the study (n=54; p<0.001).

5) Additionally, in the group with 29 women who had received 'only algorithm-based medicines' at the 5th follow-up visit, 15 were identified as responders (51.8%), while in the group with 16 women who had received 'also non-algorithm-based medicines', 5 were identified as 'responders' (31.3%). Data of 45 women with complete diaries and prescription reports at the 5th follow-up were evaluated.

6) At the end of the study, 28 out of 51 women (36.4%) with valid scores at the AGOS for symptoms reported a score of +2 (associated with moderate improvement) or more, while 10 out of 52 reported +2 or more at the AGOS for general health (24.7%). All intermediate and final outcomes of the AGOS for symptoms and AGOS for general health are listed in Table 6.

7) We found a significant correlation between the course of PMS scores and the AGOS for symptoms (Spearman's correlation coefficient -0.4, p<0.001) as well as a borderline significance on correlation between the changes in PMS scores and the AGOS for general health (Spearman's correlation coefficient -0.12, p=0.054).

Homeopathic medicines used

Overall, 43 different homeopathic medicines were prescribed during the study, mostly for PMS/S symptoms, sometimes for additionally treating inter-current, acute complaints or a general condition. In Table 7 details of homeopathic medicines that were used in the study are presented.

Potency and dose

The following potencies were used: D12, C30, C200, 30K, 200K, MK, XMK, Q1, Q3, Q6, Q12 (see: List of abbreviations). Repetition varied from daily doses with D12 or low Q-potencies, to once per week, or every two, four or six weeks. Sometimes women were instructed to take a dose at a particular phase of the menstrual cycle. All medicines were dispensed as granules.

Adverse Events/Aggravations

No unexpected or serious adverse reactions were reported that could be attributed to the homeopathic treatment. Several important events were reported during the study time, like death of family members, loss of work, serious illness, divorce, major surgery, admission to mental hospital and burnout. In some cases these events led to termination of participation (Figure 2, reasons for dropout). In 26 cases, doctors reported mild, transient aggravation of symptoms that could be explained as an initial reaction to the homeopathic medication. In 4 participants, old symptoms returned and disappeared again during the course of the treatment. Initial aggravations and return of old symptoms are commonly observed during homeopathic treatment [24]. 3 women dropped out after their symptoms had worsened: 1 suffered from a burnout and it is unclear if the aggravation of symptoms could be attributed to the homeopathic medicine; 1 had only mild symptoms that improved by 50%, but acne worsened; 1 reported improvement of physical symptoms but deterioration of mental symptoms and she consulted a psychologist.

Discussion

In this study, the utility of a previously designed and tested questionnaire and algorithm for semi-standardized individualized homeopathic treatment of women with PMS/S with 11 medicines was confirmed in 77 women with 9 months' follow-up, with promising results. The use of this questionnaire and algorithm could be recommended to facilitate further clinical research about homeopathic treatment of women with PMS. With the non-randomized study design it was not possible to evaluate efficacy of the 11 selected medicines.

Considerations about the semi standardized treatment

Almost half (47.2%) of the first algorithm-based prescriptions remained stable throughout the 9 months' study period in women who completed the study. This could indicate that in these women the medicine selection by the algorithm was considered accurate by the treating doctor. This finding is meaningful, because in this study, with 11 medicines and strict criteria for the first prescription, the first homeopathic medicine selection might have led to inaccurate 'individualized' homeopathic prescriptions in a considerable (beforehand unknown) proportion of the participating women. The increase in non-algorithm-based prescriptions at the 3rd follow-up visit supports this last assumption. The association between 'overall prescription category' and results was evaluated by qualitative, descriptive and by quantitative analysis. Relatively more 'responders' were found in the group who had used 'only algorithm-based

Medicines prescribed	First visit		Follow-up 1		Follow-up 2		Follow-up 3		Follow-up 4		Follow-up 5		Follow-up 6	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sepia officinalis	19	*24.7*	15	*21.7*	16	*24.2*	16	*25.4*	9	*17.3*	9	*16.1*	7	*13.4*
Natrium muriaticum	14	*18.2*	10	*14.5*	8	*12.1*	5	*7.9*	7	*13.5*	6	*10.7*	7	*13.4*
Lilium tigrinum	11	*14.3*	10	*14.5*	7	*10.6*	9	*14.3*	9	*17.3*	10	*17.9*	11	*21.1*
Cimicifuga racemosa	6	*7.8*	7	*10.1*	6	*9.1*	7	*11.1*	4	*7.7*	2	*3.6*		
Lachesis mutus	6	*7.8*	5	*7.2*	2	*3.0*	3	*4.8*	3	*5.8*	2	*3.6*	2	*3.8*
Magnesium carbonicum	6	*7.8*	5	*6.5*	4	*6.1*	3	*4.8*	3	*5.8*	3	*5.4*	3	*5.8*
Magnesium phosphoricum	6	*7.8*	4	*5.2*	5	*7.6*	4	*6.3*	3	*5.8*	3	*5.4*	2	*3.8*
Phosphorus	3	*3.9*	2	*2.6*	2	*3.0*	2	*3.2*			1	*1.8*	1	*1.9*
Calcarea carbonica	1	*1.3*			3	*4.5*	3	*4.8*	4	*7.7*	3	*5.4*	3	*5.8*
Lac caninum	1	*1.3*	1	*1.4*			1	*1.6*	1	*1.9*	2	*3.6*	1	*1.9*
Pulsatilla pratensis	1	*1.3*	2	*2.9*	1	*1.5*	2	*3.2*	2	*3.8*	2	*3.6*	2	*3.8*
Lycopodium clavatum	1	*1.3*												
Nux vomica	1	*1.3*	1	*1.4*	1	*1.5*	1	*1.6*	1	*1.9*	3	*5.4*	2	*3.8*
Natrium carbonicum	1	*1.3*	1	*1.4*	1	*1.5*	1	*1.6*	1	*1.9*	1	*1.8*	2	*3.8*
Folliculinum			2	*2.9*	2	*3.0*							1	*1.9*
Tuberculinum					1	*1.5*	1	*1.6*	1	*1.9*	1	*1.8*	1	*1.9*
Chamomilla					1	*1.5*	1	*1.6*						
Carcinosinum							1	*1.6*	2	*3.8*	1	*1.8*	1	*1.9*
Staphysagria									1	*1.9*	1	*1.8*		
Samarium muriaticum											1	*1.8*	1	*1.9*
No medicine prescribed	0		3		4		1		2		0		5	
Missing/dropout	0		8		11		14		25		21		25	
Total analysed	77		69		66		63		52		56		52	

Table 7: Homeopathic medicines used in the study.

medicines' compared to the group who had used 'also non-algorithm-based prescriptions'. However, after estimation of changes in mean PMS scores, no statistical significant differences were found between the groups with 'only algorithm-based' versus 'also non-algorithm-based' homeopathic medicines. To compare this semi-standardized treatment to 'unrestricted' individualized treatment (according to the personal analysis of the homeopath) would require a different study design.

Dropouts

It was evaluated what proportion of the women who dropped out, had experienced no improvement or deterioration of symptoms. Of the 23 dropouts, 7 women (30.4%) reported 'improvement of symptoms' at the time of dropout (AGOS: +1, +2, +3 or +4), 6 (26.1%) reported 'no change/unsure' (AGOS=0) and 7 (30.4%) reported 'deterioration' (AGOS: -1, -2, -3 or -4). 3 women (13.0%) dropped out before the first follow-up visit and did not complete the first AGOS questionnaires.

Duration of follow-up

In 16 women, the follow-up duration was more than 9 months. This could be due to lengthy menstrual cycles, planning problems or holidays. Several women who completed 9 months had missed at least one intermediate follow-up visit. We would define their last visit as the 6th follow-up and report missing data at the 5th follow-up (7 months). This explains why we have more missing data at the 5th than at the 6th follow-up. The lengthy follow-up may have contributed to the overall high dropout rate (22% after 3 months, 30% at the end).

Course of individual premenstrual symptoms

The mean scores of most of the 12 individual pre-defined symptoms (Table 1) gradually declined throughout the study, except for the symptom 'pain or swelling of breasts'. The mean score of this symptom decreased, but returned to baseline levels at the end of the study. In general, without a control group, we cannot know which proportion of any symptom improvement might be attributed to regression to the mean or to specific or non-specific treatment effects.

Use of medication and absence from work

Women also reported about use of additional (conventional) medication and loss of work days. Some women not only reported the use of medication for PMS symptoms, but also for other complaints, such as flu or post-operational pain. Based on this inadequate reporting, we can draw no conclusions about changes in use of additional medicines for PMS symptoms during the study, even where we observed a considerable decline. Neither could evaluation of loss of work days lead to conclusions, because of small numbers: only 5 women reported absence from work because of PMS symptoms at baseline.

General health

At the end of the study, 12 women reported 'major improvement of general health' or 'cure' by the AGOS for general health, as can be observed in table 6 (23.1%; n=52). A borderline significant association was found between mean changes in PMS scores and AGOS for general health. Not all women, whose premenstrual symptoms improved, reported improvement in general health additionally. This was also observed in the previous pilot study, where several participants whose premenstrual symptoms improved, explained they had enjoyed excellent general health before the start of the study and this had not changed.

Positioning this research

For research about individualized homeopathic interventions in specific clinical conditions, like PMS, various pieces of evidence are required. Efficacy of specified homeopathic medicines in controlled conditions as well as effectiveness of well-defined homeopathic

interventions in daily practice should be evaluated. Yakir et al. explored the efficacy of specified homeopathic medicines compared to placebo in semi-standardized individualized homeopathic treatment of women with PMS in controlled conditions [14]. The Dutch research line focused on pragmatic research, to evaluate the effectiveness of a homeopathic intervention with semi-standardized medicine selection. This homeopathic treatment was as close to 'real life' homeopathic practice as possible, within the limitations of the study design. The results of pragmatic trials are more generalizable than those of explanatory trials [25].

In October 2012, as a next step, the present research group started an international pilot study in the Netherlands, Germany and Sweden, to investigate the feasibility of organizing a large pragmatic randomized controlled trial.

Conclusions and Recommendations

A semi-standardized algorithm for individualized homeopathic treatment of women suffering from PMS/S with 11 medicines proved useful in daily homeopathic practice. Restrictions for the first prescription improved reproducibility of the treatment. The proportion of algorithm-based prescriptions declined during the study, but was still 68.8% at the 3rd follow-up and 64.3% at the 5th follow-up. At the end point (≥ 8 months follow-up), a clinically relevant improvement of premenstrual symptoms had occurred in 57.5% of the analyzed group (n=52) and in 39% of women who were included (n=77). Additionally, the mean decline in premenstrual symptoms throughout the study was statistically significant. Significantly more women with mild PMS symptoms dropped out (compared to women with moderate to severe symptoms), as well as women with a psychiatric history other than PPD (compared to women without a psychiatric history). These outcomes could have implications for inclusion or exclusion of these groups in future research.

The PMS algorithm could be used in follow-up research about PMS treatment in other settings. A shorter duration of follow-up would be recommended to limit dropout rates. To diminish the proportion of missing diaries, online diaries could be used. If the algorithm-based treatment for PMS is validated in controlled clinical trials, it could be implemented in primary care for women with premenstrual disorders. Similar semi-standardized types of homeopathic treatment could be tested for other relevant clinical conditions.

Acknowledgement

The study was sponsored by the Dutch medical research organization ZonMw, the Dutch patients/ consumers organization Koninklijke Vereniging Homeopathie Nederland (KVHN), VSM Geneesmiddelen BV, Alkmaar, the Netherlands (who provided the registered medicines used in the study) and the Louise van Eeghen Stichting. All medicines were delivered free of postal charge by the Hahnemann Pharmacy, Heiloo, the Netherlands. We wish to thank the participating women, the participating homeopathic doctors and the (previous) Dutch Association of Homeopathic Doctors (VHAN) for secretarial and administrative support. We also thank Daniëlle van der Windt (previously at EMGO-institute for research in primary care, Vrije Universiteit Medical Center (VUMC), Amsterdam, presently at Institute for Primary Care and Health Sciences, Keele University, UK) for her expert help to set up the study, Robert Mathie (British Homeopathic Association) for his helpful critical comments on the manuscript and Annet van den Berg (independent designer) for the excellent infographics.

Ethical approval: METc VUmc registers nr. 2007/139 dd. 6-9-2007

Trial register: Nr. NL17805.029.07

References

1. Halbreich U, Backstrom T, Eriksson E, O'Brien S, Calil H, et al (2007) Clinical diagnostic criteria for premenstrual syndrome and guidelines for their quantification for research studies. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology. 23: 123-130.
2. O'Brien PM, Backstrom T, Brown C, Dennerstein L, Endicott J, et al. (2011) Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: the ISPMD Montreal consensus. Archives of women's mental health.14: 13-21.
3. Mishell DR (2005) Jr. Premenstrual disorders: epidemiology and disease burden. The American journal of managed care 11: S 473-479.
4. Heinemann LA, Minh TD, Filonenko A, Uhl-Hochgraber K (2010) Explorative evaluation of the impact of severe premenstrual disorders on work absenteeism and productivity. Women's health issues: official publication of the Jacobs Institute of Women's Health 20: 58-65.
5. Marjoribanks J, Brown J, O'Brien PM, Wyatt K (2013) Selective serotonin reuptake inhibitors for premenstrual syndrome. Cochrane Database Syst Rev 6: CD001396.
6. Shah NR, Jones JB, Aperi J, Shemtov R, Karne A (2008) Selective serotonin reuptake inhibitors for premenstrual syndrome and premenstrual dysphoric disorder: a meta-analysis. Obstetrics and gynecology. 111: 1175-1182
7. Lopez LM, Kaptein AA, Helmerhorst FM (2012) Oral contraceptives containing drospirenone for premenstrual syndrome. Cochrane database of systematic reviews 2: CD006586.
8. Freeman EW, Rickels K, Sammel MD, Lin H, Sondheimer SJ (2009) Time to relapse after short- or long-term treatment of severe premenstrual syndrome with sertraline. Archives of general psychiatry 66: 537-544.
9. Halbreich U (2008) Selective Serotonine Reuptake Inhibitors and Initial oral contraceptives for the treatment of PMDD: Effective but not enough. CNS Spectr 13: 566,569-572.
10. Sundstrom-Poromaa I, Bixo M, Bjorn I, Nordh O (2000) Compliance to antidepressant drug therapy for treatment of premenstrual syndrome. J Psychosom Obstet Gynaecol, 21: 205-211.
11. Freeman EW (2010) Therapeutic management of premenstrual syndrome. Expert opinion on pharmacotherapy 11: 2879-2889.
12. Yakir M, Kreitler S, Brzezinski A, Vithoulkas G, Oberbaum M, et al (2001) Effects of homeopathic treatment in women with premenstrual syndrome: a pilot study. Br Hom J 90: 148-153.
13. Lepaisant C (1995) Clinical trials in homeopathy: treatment of mastodynia due to premenstrual syndrome. Rev Fr Gynecol Obstet 90: 94-97.
14. Chapman EH, Angelica J, Spitalny G (1994) Strauss M. Results of a study of the homeopathic treatment of PMS. J Am Inst Hom 87: 14-21.
15. Komar T, Peck KS, Torline JR, Deroukakis M (2006) A qualitative study to determine the efficacy of the homeopathic simillimum in the treatment of premenstrual syndrome. Am J Hom Med 99: 196-204.
16. Fäustle R (1992) Behandlung des prämenstruellen Syndroms mit einem homoöpathischen Kombinationspräparat. Biol Med 6: 423-426
17. Martinez B (1990) Folliculinum: Efficacy in premenstrual syndrome. Br Hom J 79: 104-105.
18. Laister, C-A (2008) The efficacy of homoeopathic simillimum in the treatment of premenstrual syndrome (PMS). PhD thesis. Department of Homoeopathy, Durban Institute of Technology .
19. Danno K, Colas A, Terzan L, Bordet MF (2013) Homeopathic treatment of premenstrual syndrome: a case series. Homeopathy 102: 59-65.
20. Klein-Laansma CT, Jansen JCH, van Tilborgh AJW, Van der Windt DAWM, Mathie RT, et al (2010) Semi-standardised homeopathic treatment of premenstrual syndrome with a limited number of medicines: Feasibility study. Homeopathy 99: 192-204.
21. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2006 on the Community Code relating to the Medicinal Products for Human Use.
22. Borenstein JE, Dean BB, Leifke E, Korner P, Yonkers KA (2007) Differences in symptom scores and health outcomes in premenstrual syndrome. J Women's Health 16: 1139-1144.
23. Rossi E, Bartoli P, Bianchi A, Endrizzi C, Da Frè M (2012) Homeopathic aggravation with Quinquagintamillesimal potencies. Homeopathy 101: 112-120.

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

25. Witt CM (2009) Efficacy, effectiveness, pragmatic trials--guidance on terminology and the advantages of pragmatic trials. Forschende Komplementarmedizin 16: 292-294.