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CLINICAL

Semi-standardised homeopathic treatment of premenstrual syndrome with a limited number of medicines: Feasibility study

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Background: **Individualised homeopathy involves a large number of possible medicines. For clinical research purposes it is desirable to limit this number, create more consistency between prescribers and optimising the accuracy of prescription. Using a semi-standardised treatment protocol, we aimed to improve homeopathic management of targeted subgroups of women with premenstrual syndrome/symptoms (PMS/S).**
Objectives: **To design a semi-standardised protocol for individualised prescribing in PMS/S with a limited number of homeopathic medicines, and to explore the feasibility of working with it in daily homeopathic practice.**
Methods: **With help of an expert panel, homeopathic medicines were selected, as well as predictive symptoms and characteristics (keynotes) for each medicine. With those, we designed a patient questionnaire and a diagnostic algorithm. The patient questionnaire contained 123 questions, representing potential predictive symptoms for 11 homeopathic medicines for PMS/S. The medicines selected (in rank order) were *Sep, Nat-m, Lach, Cimic, Lac-c, Puls, Calc, Lil-t, Mag-p, Mag-c, Phos.***
In a feasibility study 20 homeopathic doctors used the protocol in daily practice. The diagnosis was confirmed by daily rating of pre-defined symptoms during two consecutive menstrual cycles. The acceptability and feasibility of the protocol were evaluated after 3 months follow-up, at which time we also measured changes in premenstrual symptom scores and patient-reported changes in symptoms and general health.
Results: **The doctors mostly complied with the protocol and valued the computerised diagnostic algorithm as a useful tool for homeopathic medicine selection. 33 patients completed 3 months follow-up. By then, 19 patients still taking the first medicine on the basis of the algorithm. We received valid symptom records of 30 patients. Premenstrual symptom scores dropped by 50% or more in 12 patients and by 30–50% in 6 patients; scores dropped by less than 30% or increased in 12 patients. Recruitment of patients (n = 38 in 9 months) proved difficult. Adherence to the diaries and the questionnaire was satisfactory.**
Conclusions: **It is feasible to use a semi-standardised protocol for individualised homeopathic prescribing in PMS, in daily practice. Its predictive value and the percentage of women with PMS/S helped by the selected medicines remain to be evaluated in further research. In future research, active promotion will be needed to recruit patients.**
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Keywords: Diagnostic algorithm; Expert panel; Feasibility study; Homeopathy; Predictive value; Premenstrual symptoms; Premenstrual syndrome; Questionnaire

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Introduction

Premenstrual syndrome/symptoms (PMS/S)

Premenstrual syndrome (PMS) is characterised by the cyclic occurrence of symptoms disturbing normal daily functioning during the luteal phase of the menstrual cycle.[1] In psychiatry, premenstrual dysphoric disorder (PMDD) is diagnosed.[2] Prevalence rates of PMS and PMDD ranging from 8% to 32% are reported.[3] Because of different methodologies and diagnostic criteria, prevalence rates of premenstrual symptoms and PMS vary widely between different studies.[3] In some studies it is estimated that 85% of the women of reproductive age have one or more premenstrual symptoms and about 30–40% of these women seek help from their General Practitioner (GP).[4,5] In a Dutch survey among 997 women having menstrual periods, 3.9% reported at least five (emotional and physical) premenstrual symptoms.[6] These women experienced more problems in daily activities and assessed their mental and general health as inferior to that of women without PMS. Other researchers report 1–7 missed working days in a year because of premenstrual symptoms, and an average of 7 days per month with 50% less productivity.[7,8]

Over 300 therapies have been proposed for PMS.[2] In the past, progestagens were the most prescribed conventional medicines, but this therapy is not supported by evidence.[9] More recently some good evidence has come forward for the treatment of severe PMS with selective serotonin re-uptake inhibitors (SSRIs).[10] However, many women prefer other therapies for several reasons: in a Swedish study reasons for discontinuing therapy with antidepressants for PMS were adverse (43%), a wish to deal with the problems 'naturally' (23%), fear of dependence (19%), not wanting to take these drugs (20%), or other reasons.[11] It seems worthwhile to investigate the effectiveness of homeopathic treatment in women with PMS/S. On homeopathic treatment of PMS a few studies of variable design have been published in the literature.[12–16] In an Israeli pilot study PMS symptoms declined significantly in women who had individual homeopathic treatment, compared to placebo.[13]

Research challenges

Individualised homeopathy can involve a wide variety of medicines for PMS/S. Treatment involves the whole person, not only the actual clinical condition. Patients with premenstrual symptoms often have other health problems. These circumstances create challenges for research methodology and design. For research in individualised homeopathy we consider it important to:

a. limit the number of homeopathic medicines,
b. optimise prescription of homeopathic medicines for PMS/S,
c. create more consistency between prescribers.

Research objectives

a. To select a limited number of homeopathic medicines that are relatively frequently used for homeopathic treatment of PMS/S (preferably medicines with an incidence of at least 5% of the prescriptions in the population of women with PMS/S who consult a homeopathic physician), with favourable results. With such a list of medicines we could target subgroups of women with PMS/S, who are likely to respond well to homeopathic treatment.
b. To develop an accurate patient questionnaire to differentiate between the relevant homeopathic medicine subgroups. The questions represent potential predictive symptoms and characteristics (keynotes) of the selected homeopathic medicines,
c. To design a homeopathic diagnostic algorithm for PMS/S in accordance with the questionnaire, suggesting medicines for the relevant subgroups,
d. To explore the feasibility of working with this diagnostic protocol in daily homeopathic practice in a prospectively recruited sample of women with PMS/S.

Part 1: stepwise design of the treatment protocol

Delphi procedure and focus groups

For the expert panel we recruited 8 experienced homeopathic doctors, most of whom had previously been involved in research projects. To select homeopathic medicines for treatment of women with PMS/S (step 1) and potential predictive symptoms and characteristics (step 2), we organised Delphi rounds by e-mail and focus group meetings. The Delphi method facilitates communication between and among a panel of experts, to reach consensus about complex problems through convergence of opinion.[17] When experts have similar training and knowledge, a relatively small number of experts should give reliable and stable outcomes.[18] Focus group meetings stimulate interaction between the members of an expert panel.[19] All experts received data and background information before every round. During the Delphi procedure, we asked the experts not to communicate with each other about the issues at stake. They sent their opinion to the researchers independently. For each step we considered the Delphi round complete when sufficient consensus was reached to organise a conclusive focus group meeting. The focus group meetings were videotaped.

Background information for the expert panel

To select homeopathic medicines for PMS/S and potential predictive symptoms/characteristics, the experts could use relevant information from the Israeli pilot study (see above) and a subsequent Randomised Controlled Trial (RCT) on the homeopathic treatment of PMS (unpublished as yet), registration, data collection and materia medica validation projects.[20] We extracted relevant data from the Dutch HARP-project (Homeopathic Administration and Registration Program) and the results of the VHAN (Dutch Homeopathic Physicians Organisation) Commission for Methods and Validation.[21–24] We also sought the opinions of two external advisers, Yakir and Relton. Finally, the experts could consult the homeopathic

literature, repertories, materia medica, case reports and use their own practical experience. The experts reported on standardised forms. They always had to justify their decision and indicate the sources(s) they had used (Figure 1).

Step 1. Selecting homeopathic medicines

In the first Delphi round each expert could freely select 10 medicines for treatment of PMS/S. In subsequent rounds we progressively narrowed the range of medicines, depending on the outcome of the previous round. At a focus group meeting the experts achieved consensus on 10 medicines. They suggested organising one last Delphi round (a so called 'losers round'), to select one more. The final list of 11 medicines was (in rank order of selection): *Sep*, *Nat-m*, *Lach*, *Cimic*, *Lac-c*, *Puls*, *Calc*, *Lil-t*, *Mag-p*, *Mag-c*, *Phos*. There were a few less obvious medicine choices:

a. We excluded *Foll* (*Folliculinum*). The two external experts and other authors suggested that *Foll* might play an important part in treatment of PMS.[12,25–27] We did not select it, however, because *Foll* is an not registered in the Netherlands and most of our experts had no experience with it.
b. We included *Mag-p* and *Mag-c*. In daily practice, these medicines are better known as remedies for menstrual cramps than for premenstrual symptoms. However, *Mag-p* and *Mag-c* are associated with symptoms like common cold or sore throat before menses. In one study of premenstrual symptoms this condition had a prevalence of 10% among the women in the target group.[28] In extended prospective research we hope to assess the value of these medicines for treatment of PMS/S.

Step 2. Selecting potential predictive symptoms per medicine

For the patient questionnaire we needed predictive symptoms and characteristics for the 11 medicines, that could also differentiate between them. In consecutive Delphi rounds, we asked the experts to select such symptoms for each medicine and to grade the importance of each symptom in predicting the response to treatment, on a scale of 1–3: 1 = not very important; 2 = important; 3 = very important, essential. All symptoms were categorised and listed. During the second focus group meeting the symptoms were discussed. The experts reached consensus about final lists of 7–10 symptoms for each medicine. We list them in Table 1.

Step 3. Designing the patient questionnaire

The experts and researchers agreed to:

a. Design a patient questionnaire with 5 response options for each item (e.g. 1 = never, to 5 = always), to be able to discriminate between mild and severe symptoms,
b. Use premenstrual symptoms as well as physical, general and mental symptoms for the questionnaire,
c. Select symptoms that are specific for certain selected medicines, help decide between them and occur regularly in the population with PMS/S,
d. Ask some questions not in the paper questionnaire, but during consultation, because of the delicate nature of the subject (e.g. history of sexual abuse).

The questionnaire thus contained 123 questions in the following categories: 15 premenstrual symptoms; 16 menstruation symptoms; 51 general, physical symptoms; 41 psychological characteristics, 4 to be asked during the consultation. An example of questions and answering options is given in Figure 2.

Step 4. Designing a diagnostic algorithm

One of the researchers (JCHJ) designed the computerised diagnostic algorithm. It was in fact a targeted repertory for homeopathic treatment of premenstrual symptoms, limited to 11 medicines. It worked like this: the patient's answers to the 123 questions were transferred to the computerised program. The algorithm calculated total scores for each of the medicines and presented these on the screen. The algorithm thus indicated the most appropriate medicine(s) to prescribe.

Questions could contribute to the score of one or more medicines, the scoring level depending on:

a. The severity of the symptom as indicated by the patient (as shown in Figure 2). We installed cut off points to discriminate between mild, moderate and severe symptoms; only moderate and severe symptoms would score (progressively).
b. The pre-programmed weighting factor (grade) of the question-medicine-combination. We installed weighting factors to fine-tune differentiation between the medicines.

All medicines had an equal chance of being selected. Three researchers and four experts refined and tested the program. We wrote detailed instructions for the doctors how to apply the algorithm.

Part 2: the feasibility study

Methods

Ethical approval and informed consent: The Medical Ethics committee (METc) of the Vrije Universiteit Medical Center approved the study protocol. Participating patients received written information before the interview and were invited to provide informed consent. After the interview they were given at least 24 h before being invited to sign the informed consent form. They were given the opportunity to consult an independent doctor about the study.

Recruitment of doctors: We recruited doctors by calls in the Journal of the VHAN, *Similia Similibus Curentur (SSC)*, by e-mailing all VHAN members and through the VHAN website (www.vhan.nl). We also presented the project at an educational conference for Dutch homeopathic doctors.

Recruitment of patients: Patients were recruited by an article in the largest Dutch newspaper and some local newspapers, by letters to general practitioners and by launching a website about the project. Women who indicated interest received a package by mail, with information about the

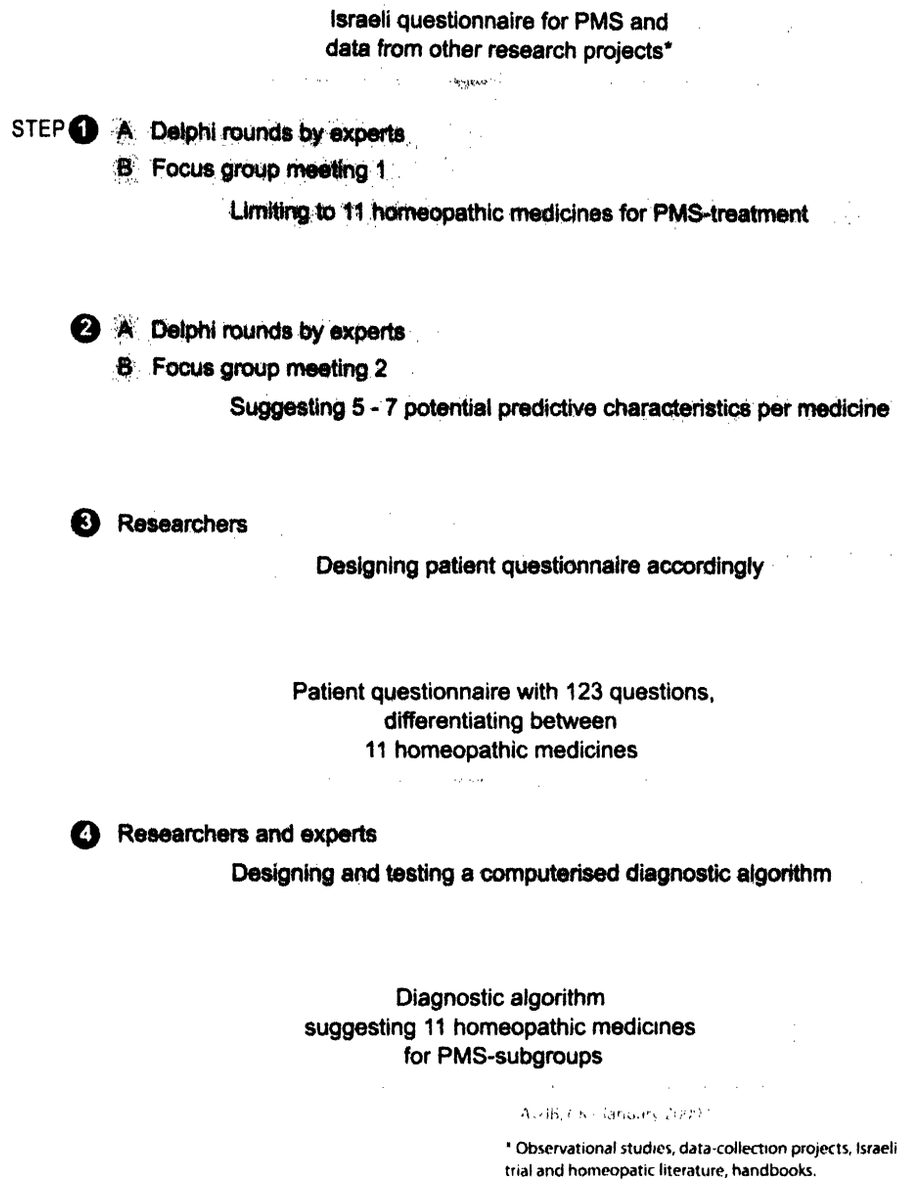

Figure 1 Flow chart part 1: stepwise design of the PMS treatment protocol.

project, informed consent forms and names and addresses of participating doctors.

Inclusion and exclusion criteria: The treating physicians interviewed women who were interested in participation, to assess eligibility. Inclusion criteria were: (1) a premenstrual symptom pattern; (2) age 18–50 years. Exclusion criteria were: (1) wish to get pregnant during the time of the study; (2) use of antidepressants or hormones; (3) other treatment for PMS/S (except incidental use of painkillers or tranquilizers on single days); (4) recent homeopathic treatment for any disorder. Women who used oral contraceptive pills (OCPs) or intra-uterine contraceptive devices (IUCDs), and still had a premenstrual symptom pattern, were included and identified as a separate group (different types of IUCDs were identified). We allowed the use of conventional medicines, except the excluded categories. If they were taken for premenstrual symptoms, for example painkillers for headache, we used them as a secondary outcome measure (see below).

PMS or premenstrual symptoms: Prospective daily rating of mood and physical symptoms is widely used to diagnose PMS or premenstrual symptoms.[4,29] Therefore, after recruitment, we asked the women to keep premenstrual symptom-diaries for two consecutive menstrual cycles, to confirm the diagnosis. We asked patients to score predefined symptoms (range 1–10) daily. If there was a clear premenstrual pattern of at least one symptom, the woman could be included and enrolled in the diagnosis category PMS or premenstrual symptoms. We used the International Classification of Primary Care (ICPC)-2 criteria for PMS (code X89) and premenstrual symptom/complaint (code X09). Criteria for PMS are a cyclic occurrence in the menstrual cycle of two or more of the following symptoms during each of two consecutive

Table 1 Symptoms and characteristics, selected by the expert panel

Sepia officinalis
- Frequent discharge from vagina
- Pain in the abdomen with a heavy, bearing down sensation, as if the organs bulge out
- Easily irritated, irritable
- Mental improvement after vigorous physical exertion, like sports or dancing
- Cold sores (Herpes simplex) around the lips
- Indifference towards family and friends; tendency to withdraw
- Low back pain, easing when supporting the back with a cushion
- Diminished libido before menstruation

Natrium muriaticum
- Does not show grief or being hurt
- Symptoms started after grief
- Love of salt
- Headache
- Symptoms caused by sun, such as headache or eruptions
- Cold sores (Herpes simplex) around the lips
- When grieving, does not want to be consoled, prefers to be alone
- Low back pain, easing when supporting the back with a cushion

Pulsatilla pratensis
- Weeps easily
- Quickly changing moods
- Distaste of fatty food; complaints of stomach or bowel by fatty food
- Desires fresh air, to be in open air
- Needs comforting when grieving
- Little thirst
- Bleeding during menstruation fluctuates
- Mild, yielding disposition
- Symptoms caused by sun and warmth

Lachesis mutus
- All symptoms improve after onset of menstrual bleeding
- Does not tolerate tight clothing around the neck, like a tight collar
- Very talkative
- Flushes of heat
- Head feels too hot
- Left-sides symptoms
- Jealousy
- Symptoms start or worsen during sleep or on waking

Calcarea carbonica
- Coldness of feet
- Tense, painful or swollen breasts
- Pain or bleeding during the menstrual period gets worse by physical exercise or emotions
- Menstrual bleeding returns by vigorous physical exercise or emotions, after it had stopped
- Various fears
- Sensitive to the opinion of others
- Tendency to put on weight easily
- Even when very tired, finishes the job she is working on
- Desire for eggs

Lac caninum
- Tense, painful or swollen breasts
- Common cold of the nose, pain in the throat, hoarseness or cough before menstruation
- Pains switch form the right side of the body to the left side and the other way around
- Lack of self-confidence
- Dizziness and/or an unsteady floating sensation; sensation of fainting
- Loves spicy food
- Abdominal pain during ovulation
- History of sexual abuse

Cimicifuga racemosa
- Restless, wild or confused feeling in head
- Heavy or depressed feeling
- Pain during menstruation gets worse when the bleeding increases
- Talkative
- Complaints of neck and/or back
- Pain in the hips
- Frequent sighing
- Headache with a dull of dizzy feeling in the head
- Sensitive to pain, noise or other external impressions

Table 1 (*continued*)

Lilium tigrinum
- Pain in the abdomen with a heavy, bearing down sensation, as if the organs bulge out
- The bleeding at menstruation stops when resting or lying and gets worse when walking
- Abdominal pain during ovulation
- Feeling hurried, agitated, chaotic, as if you have to do all kinds of things at once
- Easily irritated, irritability
- High sexual desire
- Fear of being forsaken; feeling of being forsaken
- Conflict between sexuality and morality

Magnesium phosphoricum
- Abdominal cramps during menstruation or other than during menstruation
- Abdominal pains eases by being massaged or by drawing up the legs
- Facial pain or other nerve pains
- Toothache before menstruation
- Pain eases by applying a hot water bottle or by warm surroundings and gets worse by cold
- Applications or cold air
- Sensitive to quarrels
- Muscle cramps
- Restlessness before menstruation

Magnesium carbonicum
- Weak or not refreshed in the morning, on waking; bad mood in the morning
- Tired, exhausted before and during menstruation
- Common cold of the nose, pain in the throat, hoarseness or cough before menstruation
- Bleeding during menstruation stops when walking, in daytime, and returns when resting, lying or at night
- Sensitive to quarrels
- Loves vegetables or loathes vegetables
- Stomach complaints

Phosphorus
- Much thirst
- Loves cold drinks
- Nasal bleeding, bruises, prolonged bleeding of wounds
- During menses prolonged bleeding (at least one week), bright red
- Intensely sympathises with others, cares a lot about others
- Fear of thunder, of being alone, of dark
- Open, connecting easily
- Loves company of other people

cycles: peripheral oedema; breast tenderness/swelling; headache; irritability; mood changes. The ICPC-2 criteria for premenstrual symptom/complaint are not specified concerning the number or character of the symptoms. We defined it as a cyclic occurrence of at least one premenstrual symptom during two consecutive cycles and the criteria for X89 are not met. As part of the feasibility evaluation, we included different categories of patients: women with a clear-cut PMS, women with a single premenstrual symptom without co-morbidity, and women with PMS/S who also suffered from other conditions unrelated to menstruation, such as fatigue or joint pains.

Using the patient questionnaire: After confirmation of the diagnosis by the treating doctor, women made an appointment for the first homeopathic consultation. They received the patient questionnaire by post, completed it and sent it back to the doctor, several days prior to the first appointment. The doctor transferred the questionnaire responses to the computerised diagnostic algorithm.

I Symptoms and complaints before menstruation

Check the most appropriate box

1 = never or almost never
2 = sometimes
3 = moderately often
4 = very often
5 = always or almost always

	Before menstruation, how often do you have ...	1	2	3	4	5
1	...pain or inflammation of the throat?			X		
2	...common cold of the nose?			X		
3	...a cough?			X		
4	...toothache?	X				
5	...breast symptoms?					X
6	...stomach symptoms?	X				

Figure 2 Extract from the questionnaire.

Applying the diagnostic algorithm: At the first homeopathic consultation, the doctors performed the history taking and examination according to standard homeopathic practice. They first analysed the case and selected a homeopathic medicine, without consulting the algorithm. Only then, the doctor asked the four questions that were not included in the paper questionnaire and transferred the responses to the computerised diagnostic algorithm. Next, the results of the algorithm were revealed. The outcome of the algorithm was a list of total scores for each of the 11 medicines; the doctor was instructed to prescribe the best scoring medicine if its total score exceeded 50 points. When the score of two or more medicines ended up 'close' (less than 20% difference between the first and next scoring medicine) the outcome was regarded as inconclusive and the doctor was asked to differentiate further, using pre-programmed additional questions.

Potencies and doses: Doctors could prescribe the potencies they usually worked with, within a certain range. Prescriptions were restricted to potencies that are considered safe according to the European act 2001/83/EC.[30] This means that no potencies below D12, 6C, 6K and Q1 would be prescribed.

Data collection at first consultation: Participating doctors recorded the patients' characteristics after the first consultation, using a pre-structured form: age, diagnosis of PMS/S, duration of symptoms/problem, age of menarche, co-diagnoses, use of conventional medicines, contraceptive methods, number of pregnancies and of live births, history of sexual abuse, post partum depression (PPD), other psychiatric illnesses. They also reported:

- the homeopathic medicine they would prescribe according to their own analysis,
- the medicine that was the outcome of the algorithm,
- the name, potency and dose of the actual prescription.

Follow-up reports: Follow-up consultations were held after 1, 2 and 3 months, preferably during or just after menstruation. The doctors were allowed to change or continue the prescription, according to their clinical judgment. They filled in a form with particulars about the prescription: potency, dose and (non-) conformity with the algorithm. If they changed the prescription, they were asked to indicate why. We evaluated how often the doctors changed the prescription. The report form contained a space for additional remarks. Separately we invited all treating doctors to report adverse events or worsening of symptoms.

Outcome measures: Primary outcome measures were:

a. Differences in premenstrual symptom scores between baseline and the third follow-up consultation. During the treatment, the patients kept a daily record of their symptoms in the premenstrual symptom-diaries. Premenstrual symptom scores were defined as the sum of daily scores of all pre-written symptoms in the diary on 14 days preceding the menstrual period.
b. A patient-reported score at the third consultation. We used an adaptation and Dutch translation of the Glasgow Homeopathic Hospital Outcome Score (GHHOS), called AGOS (Adapted Glasgow Homeopathic Hospital Outcome Score). The GHHOS rates improvement of main complaint and general well-being in a combined score, on a Likert scale ranging from −4 to +4.[31] Its successor is called ORIDL (Outcome in Relation to Impact on Daily Living).[32] The AGOS rates change in symptoms and change in general health (ranging from −4 to +4) using two separate questions: the AGOS for symptoms rates change in premenstrual symptoms, while the AGOS for general health rates change in general health.

Before every follow-up consultation the patients completed the AGOS questionnaire, to assess the change in symptoms and general health. The treating doctor collected the completed AGOS forms and sent them in, along with the follow-up reports.

Secondary outcome measures were patient-reported absenteeism of work and use of conventional medicines (e.g. painkillers) for premenstrual symptoms. These items were reported in the diaries.

Evaluation of compliance of patients: We asked the patients to complete a short evaluation form immediately after completing the questionnaire. Compliance with keeping the premenstrual symptom-diaries was measured by recording missing data.

Evaluation of (non-) concordance with algorithm and compliance of doctors: For evaluation of the doctors' compliance with the algorithm, we first assessed the frequencies of (non-) concordance between the medicine selection of the algorithm *versus* the doctor's own analysis of the case. Next, we evaluated how often the doctors prescribed a medicine that was selected by the algorithm, even if it disagreed with their own analysis. Similarly, we evaluated the prescriptions at the follow-up consultations.

The treating doctors were asked to complete a questionnaire on their views about and experiences with the protocol. Additionally we held interviews with 3 doctors. Records of these interviews were analysed by the researchers. All doctors were invited to comment on the study or make suggestions for improvement at any time.

Results

Recruitment of doctors

26 doctors initially showed interest in participating, all members of the VHAN (Dutch Association of Homeopathic Physicians), 5 of whom were general practitioners (in the Netherlands, most homeopathic doctors work on consultation basis and are not general practitioners). 4 doctors eventually declined, for a variety of reasons; 5 participating doctors received no applications from interested women during the pilot phase.

Patient recruitment

We started recruitment in October 2007. By August 1st 2008 we had sent 183 information packages. By then, 67 women had attended for an interview, 38 were included in the study, 21 were excluded and 6 were still keeping premenstrual symptom-diaries prior to inclusion (see: Figure 3). We kept no records of the women who, after receiving the information, did not make an appointment for an interview. For several women, keeping diaries during two cycles appeared to be the reason for declining. Reasons for exclusion after the diary-phase were: no premenstrual symptom pattern, serious interfering illness, largely incomplete diagnostic diaries, and insufficient motivation. One patient observed that her premenstrual symptoms had disappeared during the diary-phase and declined further participation.

Patient characteristics

We classified 30 patients with PMS (X89) and 6 with premenstrual symptom/complaint (X09); 2 could not be categorised, due to incomplete diaries. Characteristics of patients at the first consultation including co-morbidity, use of contraceptives, history of sexual abuse, PPD or other psychiatric conditions are listed in Table 2. Patients were supposed to continue their contraceptive method during homeopathic treatment. However, during the study one patient stopped taking OCPs, another patient received a copper IUCD. One patient had an (unforeseen) operation. Major life events or extreme stress due to serious problems in the family or psychological problems were reported by 5 women; 3 of them remained in the study, 2 dropped out (see next section).

Follow-up, dropout

By August 1st 2008, 38 patients were included. We evaluated the follow-up reports after 1, 2 and 3 months of homeopathic treatment. Numbers of patients who were included at the follow-up consultations are shown in Figure 3. Of the 5 patients who dropped out, 1 had not kept the diaries, 1 patient started antidepressants, 2 withdrew for relational or psychological problems (see before); 1 patient, who had only mild symptoms got an aggravation after the first prescription and withdrew.

Response of patients to the questionnaire and adherence to premenstrual symptom-diaries

Use of the patient questionnaire was satisfactory. We received 36 evaluation forms about the patient questionnaire; 2 forms were lost in the mail. 34 women thought that the questions were clear, 2 thought not; 32 found the questions easy to answer, 4 did not. 28 completed the form in less than a half-hour, 7 took more time, 1 did not know. 3 patients reported difficulties with a particular question and 6 reported unspecified difficulties with some questions. Women were generally well motivated to keep the premenstrual symptom-diaries during treatment. We received 94% of the diaries that were to be expected.

Outcomes of AGOS

The results of the AGOS at the third consultation are listed in Table 3. We assessed numbers as well as percentage of patients with valid follow-up reports after 3 months (n = 33). At the third consultation, 21 patients (**63.6%** of total) reported improvement of symptoms compared to the start of the treatment. In 15 of them (45.5%) the AGOS for symptoms was +2 or more. 9 patients (27.3%) reported no change of symptoms or were unsure about it, and 3 patients (9.1%) reported a worsening of symptoms.

The AGOS for general health showed a different pattern: 13 patients (39.4%) reported improvement of general health. 7 of these patients at baseline had co-morbidity, which could have improved. Because we did not evaluate clinical progress of co-morbidity, however, we cannot draw a firm conclusion. 11 patients reported no effect on general health or were unsure about it. Some of these patients explained that their general health had remained excellent during the study period. This is confirmed by baseline assessments: all 4 patients who reported improvement of symptoms without change in general health had no co-morbidity at baseline.

9 patients (27.3%) reported a deterioration of general health. In 3 of those patients this deterioration could be explained by intercurrent physical illness, injury or operation, in 1 by serious stress in the family; 1 had stopped taking

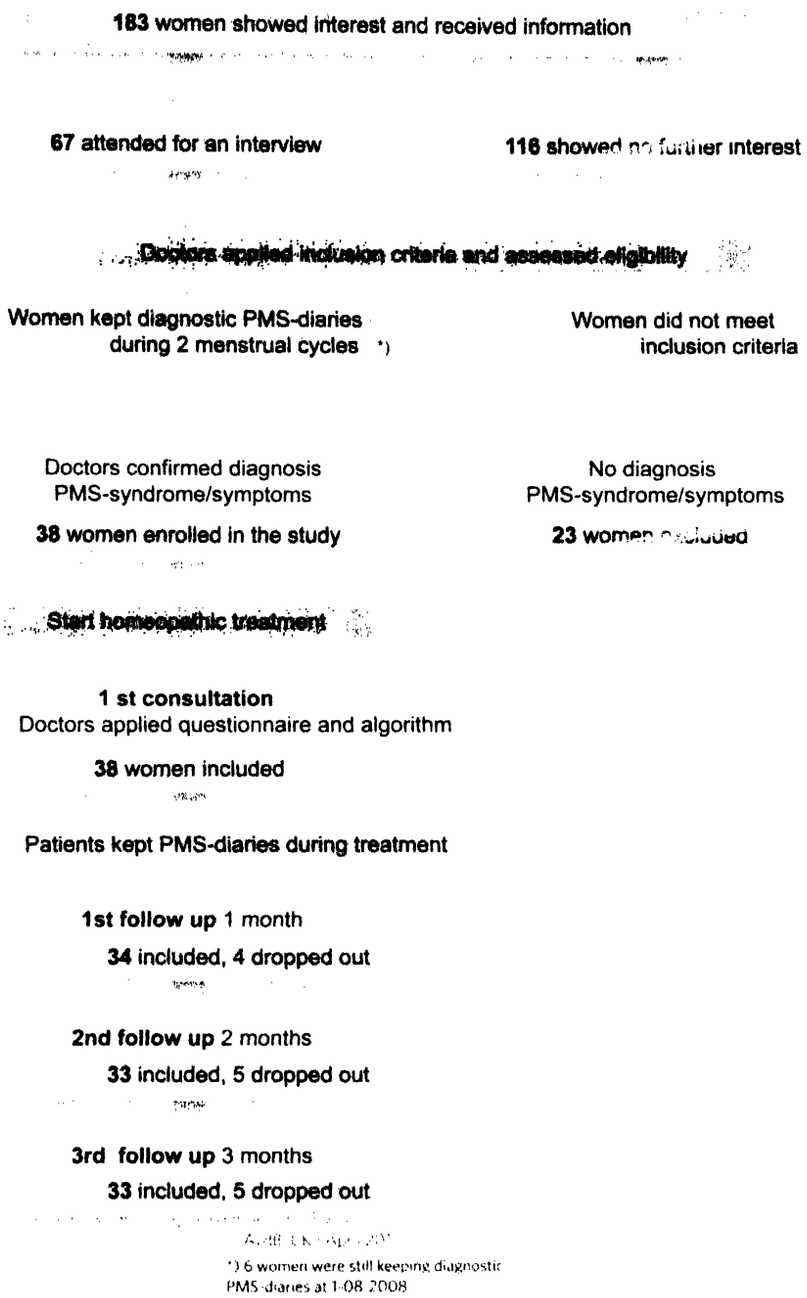

Figure 3 Flow chart part 2: feasibility study.

OCPs and 1 patient had complex problems that deteriorated during homeopathic treatment.

Outcomes of premenstrual symptom score

Premenstrual symptom scores at baseline varied widely among patients, ranging from 17 (this patient dropped out later) to 923 (this was a patient with complex problems). We received valid data from 30 patients and assessed the differences between their symptom scores at baseline and at the 3rd consultation. Some authors suggest the use of a 50% reduction in symptom ratings as a clinically relevant improvement in PMS/PMDD treatment trials *"although smaller differences may also be meaningful"*.[33] In our study, in 12 patients the premenstrual symptom score dropped by 50% or more, in 6 patients this score dropped by 30–50%. In 6 patients the symptom score change ranged from +30% through −30%. In the remaining 6 patients the premenstrual symptom score increased by more than 30% (associated with worsening of symptoms). Detailed statistical analysis of premenstrual symptom scores goes beyond the purpose of this pilot study.

Adverse events and homeopathic 'aggravations'

No serious deteriorations that could be attributed to the homeopathic intervention were reported. In 11 patients the doctors observed and reported mild, transient, worsening of symptoms after taking a homeopathic medicine. In 2

Table 2 Patient characteristics at 1st consultation (n = 38)

Patient characteristics	*N*
Age	
18–28	1
29–39	23
40–50	14
Duration of premenstrual symptoms	
0–6 months	0
6 months–1 year	0
More than 1 year	38
Diagnosis according to ICPC-2	
X89 PMS	30
X09 premenstrual symptoms	6
Not categorised	2
Contraceptive methods	
No OCPs or IUCD	27
Copper IUCD	3
Mirena IUCD	3
OCPs	3
Unknown	2
Co-morbidity (maximum 2 items per patient)	
Fatigue	4
Irritable Bowel Syndrome (IBS)	3
Back or shoulder pain	3
Allergy	2
Skin problems	2
Other diagnoses	10
Regular use of conventional medicines	13
Events in history of patients (more than 1 item possible)	
Sexual abuse	7
PPD	4
Other psychiatric conditions	6

patients, old symptoms returned and disappeared again during the course of the treatment. Both these phenomena are commonly observed in homeopathic practice. For one patient with only mild symptoms (and non-compliance with diary recording), the worsening of her symptoms contributed to her decision to discontinue participation in the study. One other patient (not included in the 11 above-mentioned) attributed a worsening of her symptoms to the homeopathic treatment, but this causality was uncertain because she also endured serious personal stress; for this reason she dropped out.

Table 3 Patient-reported changes of premenstrual symptoms and general health compared with the start of the treatment, measured at the 3rd follow-up consultation

AGOS	*Changes in premenstrual symptoms*		*Changes in general health*	
	Number of patients	*%*	*Number of patients*	*%*
+4	1	3.0	1	3.0
+3	6	18.2	1	3.0
+2	8	24.2	4	12.1
+1	6	18.2	7	21.2
0	9	27.3	11	33.3
−1	2	6.1	6	18.2
−2	0	0.0	2	6.1
−3	1	3.0	1	3.0
−4	0	0.0	0	0.0
Patients evaluated	33	100.0	33	100.0
Dropout	5		5	
Total patients	38		38	

Explanation of AGOS: +4: cured; +3: major improvement; +2: moderate improvement; +1: slight improvement; 0: no change, unsure; −1: slight deterioration; −2: moderate deterioration; −3: major deterioration; −4: disastrous deterioration.

Concordance between doctors' analysis *versus* algorithm and compliance with algorithm

The medicines that were prescribed at the first consultation are listed in Table 4 (n = 38). When the doctors agreed with the outcome of the algorithm, they logically always followed the algorithm selection (n = 16). If the algorithm outcome disagreed with their own analysis (n = 21), the doctors mostly (85%) prescribed the medicine that was selected by the algorithm (n = 18). In 3 cases they prescribed the medicine they first selected at variance with the outcome of the algorithm, because they had misunderstood the instructions. 1 doctor did not record the results of her own analysis. The numbers are too small to draw conclusions about correlations of concordance or non-concordance with type of medicine or patient subgroup.

Prescriptions during treatment

Doctors could change the prescription at the follow-up consultations, as is usual in homeopathic practice. The most frequently reported reason to do so, was: no or insufficient improvement of symptoms (n = 20; more than one change per patient possible). We evaluated the frequencies of (1) prescriptions according to the algorithm and (2) prescriptions in accordance with the doctors' own analysis. Figure 4 shows the course of these frequencies during the study. At the first consultation (n = 38), 35 patients (92.1%) were treated with a medicine that was selected by the algorithm and 3 received a prescription according to the doctor's own analysis. At the third consultation (n = 33), 23 patients (69.7%) received a medicine that was selected by the algorithm; in 19 cases (57.6%) this prescription had been unchanged since the first consultation. 10 patients (30.3%) received the doctors' own-prescribed medicine, of which 2 had been unchanged since the start of the treatment. For 3 patients, additional homeopathic

Table 4 Prescriptions at 1st consultation

Algorithm prescription		*Prescription according to the doctor's own analysis*	
Sep	10	Nux-v	1
Lil-t	6	Nat-c	1
Nat-m	5	Sep	1
Cimic	5		
Mag-p	4		
Mag-c	3		
Lach	1		
Phos	1		
Puls	1		
Calc-c	0		
Lac-c	0		
Total	35	Total	3

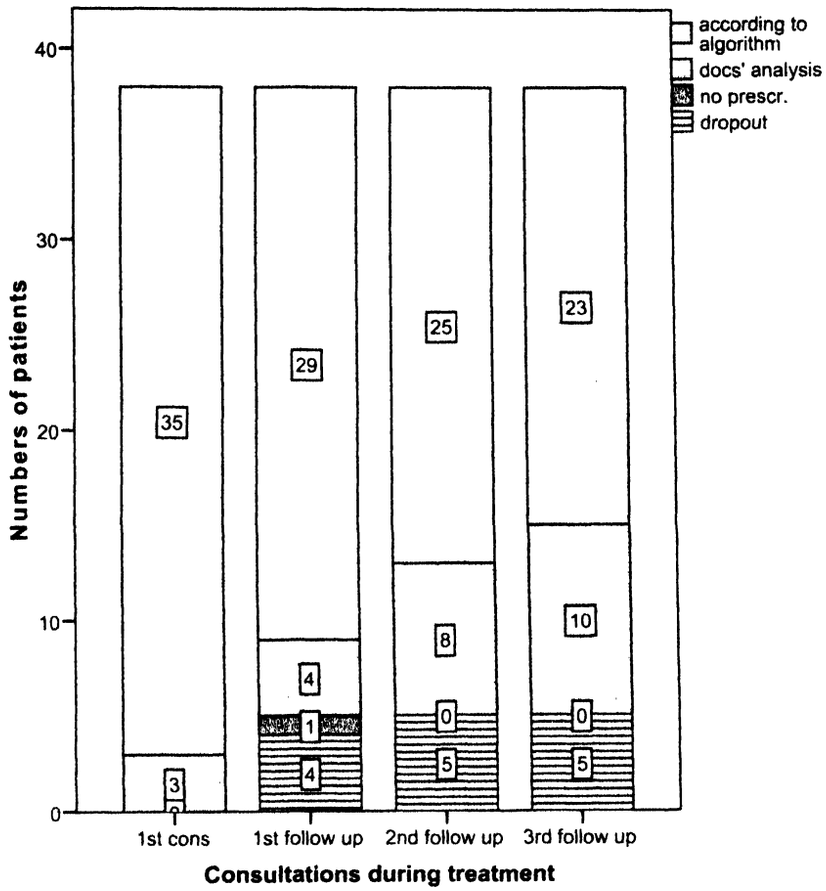

Figure 4 Frequencies of prescriptions according to the algorithm *versus* the analysis of the treating doctor, at the first consultation and during the course of the treatment (n = 38). Including dropouts.

medicines were prescribed: 1 for influenza, 1 for lower spinal injury, 1 for deterioration of general well-being.

Potencies and doses

The following potencies were used: D12, Q2, Q6, C30, 30K, 200K, MK, frequencies varying from daily (D12 and some X-potencies) to once every week (C30, 30K) or once or twice per month (MK and 200K). Sometimes instructions were given about taking a dose at a particular phase of the cycle (see also: Implications for further research).

Evaluation forms: doctors

All doctors who had sent in patient reports after 3 months follow-up were asked to fill in the evaluation questionnaire (n = 15). 12 responded, including two participating researchers (who didn't answer all the questions, or answered neutrally because of possible bias). The main results of the doctors' evaluation (n = 12) are:

- 8 thought the questionnaire and the algorithm valuable tools for homeopathic medicine selection; 4 did not answer this question
- 8 thought the protocol easy to deal with; 1 thought not; 3 did not answer
- 7 thought the protocol not conflicting with individualised homeopathy; 2 answered neutrally; 3 did not answer
- 4 thought there was enough opportunity for prescription according to the doctor's own analysis, 2 thought not, 2 answered neutrally, 4 did not answer.

Interviews with doctors

We interviewed 3 participating doctors. Two reported difficulties in scheduling the follow-up consultations, because of the periodic nature of the symptoms. This sometimes extended the period of time between two follow-up consultations. Two doctors said they would prefer more freedom to prescribe a medicine according to their own analysis of the case. Two doctors reported that their own analysis was less careful than usual, because the algorithm selected a medicine. This is a possible source of bias in the evaluation of (dis)agreement of medicine selection between the doctor's analysis and the algorithm outcome.

Doctors' additional observations and suggestions

Some doctors observed that by focusing on premenstrual symptoms, they neglected other complaints that would need attention. In agreement with this, doctors reported in two cases that premenstrual symptoms had improved, but there was no or insufficient improvement in general

health or emotional well-being. Some of the treating doctors advised against inclusion of women with complex problems, or only slight premenstrual symptoms with moderate to severe co-morbidity. They found that, in those cases, evaluation of the course of the premenstrual symptoms was too difficult. We refer to this point in: Implications for further research.

Discussion

Main findings

We succeeded in designing a concept semi-standardised protocol for homeopathic treatment of PMS/S with 11 medicines, with help of an expert panel. Working with the protocol in daily homeopathic practice proved feasible. Using this protocol we minimised inter-rater variability for the first prescription. Homeopathic doctors were flexible enough to comply with the restrictions of the protocol. They could alter the prescription at follow-up consultations and valued this possibility. Patients complied with the questionnaire and premenstrual symptom-diaries quite well. Recruitment proved difficult, due to the burden of premenstrual symptom-diaries and few referrals from general practitioners. This point is further discussed below. No major adverse events were reported.

Challenges in research on homeopathy

With this protocol for treatment of PMS/S we tried to tackle some of the challenges of clinical research in homeopathy, as outlined in the Introduction. In the treatment of PMS/S and other chronic conditions, homeopathic physicians might use up to 100 different homeopathic medicines for (groups of) women with different symptoms and different predispositions. As a consequence, the inter-rater variability in individual homeopathic prescriptions is high.[34] This complicates clinical research. Another issue is that homeopaths often fail to find the 'right' or appropriate medicine for an individual patient in their first selection.[35] The first prescribed medicine might produce no effect at all, while after treatment with a homeopathic medicine of second or third choice, the patient might very well improve. Any uncertainty in prescribing may be due to the inaccuracy of homeopathic repertories, as suggested by the research of Rutten *et al.*[36] With the development of this protocol we aimed at minimising inter-rater variability and at improving homeopathic management of women with PMS/S.

This research departed from the methods of other previous studies

In the studies that inspired our research, the researchers used a limited number of homeopathic medicines for certain clinical conditions, a patient questionnaire and/or a well-defined treatment protocol:

1. Yakir *et al.* conducted a pilot study evaluating homeopathic treatment of women with PMS, using a patient questionnaire and treating patients with a limited number of medicines (see above).[13]
2. Brigo *et al.* successfully treated migraine patients with a limited number of homeopathic medicines. They restricted inclusion of patients to those whose characteristics matched one of only 5 homeopathic medicines.[37]
3. Frei *et al.* showed that results of homeopathic treatment of children with Attention Deficit Hyperactivity Disorder (ADHD) improved after using a homeopathic diagnostic protocol including a questionnaire with potential predictive symptoms, in a cross-over trial with a long term observation period.[38,39]

Cross-cultural studies indicate that there are significant variations in the frequency of cyclical symptoms reported by different cultural groups.[40] Therefore, we developed a questionnaire with medicines and symptoms that are suitable for Dutch homeopathic practice. To minimise inter-rater variability between the participating doctors, we developed a computerised diagnostic algorithm with strict prescription rules.

Acceptability of the protocol for homeopathic physicians

The algorithm is, in fact, a mini repertory (formulary) for premenstrual symptoms, restricted to 11 medicines. In homeopathy, repertories usually contain information about symptoms from all kinds of medical conditions and all homeopathic medicines used at present. Considering that homeopathic treatment for chronic conditions is highly individualised, it was uncertain whether the homeopathic doctors would comply with the protocol, especially if the selected medicine was not their first choice. In this study, they did so. In 92% of all cases the doctors prescribed the medicine that was indicated by the algorithm at the first consultation.

Feasibility of recruitment

Recruitment of patients proved difficult. The long waiting period with keeping diaries before inclusion was a disadvantage. On the other hand, we encountered women who were desperate and highly motivated. All women who took part in the study had suffered for more than 1 year. There were few referrals by general practitioners; this may be partly due to the medical climate in the Netherlands, where many conventional general practitioners and medical specialists are opposed to homeopathy.

A future pragmatic trial would probably have to span several years to recruit sufficient numbers of eligible patients. Consideration of this factor would be influenced by the particular categories of patients that were included. Prevalence rates of PMS, PMDD and premenstrual symptoms vary widely. In one study, the prevalence of mild premenstrual symptoms was estimated at 15.6%, moderate symptoms at 67.1%, severe symptoms at 12.7% and PMDD at 4.7%.[41] Others report an estimated prevalence of PMS of 4% among women aged 15–45.[1] Participating doctors advised against inclusion of patients with complex problems or only slight premenstrual symptoms with moderate to severe co-morbidity. Restricting the research sample to severe PMS and PMDD patients without significant

co-morbidity would however reduce the number of eligible patients, and limit the applicability and generalisability of results. We recommend intense and repeated promotional activities to recruit patients.

Conclusions

It is feasible in daily practice to use a semi-standardised protocol for individualised homeopathic prescription in women with PMS/S. Doctors valued its use as a potential instrument in homeopathic diagnosis and treatment of women with PMS/S. In future research using the treatment protocol, it is advisable to restrict inclusion to patients with well-defined PMS/S, and without significant co-morbidity.

Implications for further research

A) Before a larger randomised pragmatic multi-center study using the protocol would be feasible,
   1. its predictive value for improvement of premenstrual symptoms needs to be confirmed,
   2. selected medicines and potential predictive symptoms must be evaluated,
   3. the criteria for prescription according to the algorithm *versus* prescription according to the doctors' own analysis must be evaluated,
   4. use of potencies and dosage must be evaluated as well as the opinion of doctors about strict prescription rules regarding potency, dosage and timing during the menstrual cycle,
   5. differentiated analysis between women using OCPs, different types of IUCDs, diagnosis categories X09 or X89, severe co-morbidity and other possible subgroups (to be identified) must be carried out regarding algorithm outcome, medicines prescribed, specific premenstrual symptoms and treatment results.

   These issues will be addressed in an extension of the study of the same design with more patients and longer follow-up.

B) The numbers in this pilot study are too small and follow-up too short to draw conclusions about the effectiveness of the protocol in treatment of PMS/S. More importantly, this study was not designed to assess effectiveness; a control group was not included. Its effectiveness and the percentage of women that can be treated successfully using the protocol, need to be tested in larger intervention studies, preferably in a RCT where semi-standardised homeopathic treatment would be compared with usual care.

Conflicts of interest

None of the sponsors had any influence on the study design, the selection of medicines, the collection, analysis and interpretation of the data, the results, the writing and publication of the study. The researchers, experts and participating doctors have no conflicting interests.

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