THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 00, Number 00, 2018, pp. 1–10

DOI: 10.1089/acm.2017.0388

JACM

ORIGINAL ARTICLE

Semi-Individualized Homeopathy Add-On Versus Usual Care Only for Premenstrual Disorders: A Randomized, Controlled Feasibility Study

Christien T. Klein-Laansma, MD,[1] Mats Jong, PhD,[2] Cornelia von Hagens, MD, PhD,[3] Jean Pierre C.H. Jansen, MD,[1] Herman van Wietmarschen, PhD,[1] and Miek C. Jong, PhD[1,2]

Abstract

Objectives: Premenstrual syndrome and premenstrual dysphoric disorder (PMS/PMDD) bother a substantial number of women. Homeopathy seems a promising treatment, but it needs investigation using reliable study designs. The feasibility of organizing an international randomized pragmatic trial on a homeopathic add-on treatment (usual care [UC] + HT) compared with UC alone was evaluated.

Design: A multicenter, randomized, controlled pragmatic trial with parallel groups.

Settings/Location: The study was organized in general and private homeopathic practices in the Netherlands and Sweden and in an outpatient university clinic in Germany.

Subjects: Women diagnosed as having PMS/PMDD, based on prospective daily rating by the daily record of severity of problems (DRSP) during a period of 2 months, were included and randomized.

Interventions: Women were to receive UC + HT or UC for 4 months. Homeopathic medicine selection was according to a previously tested prognostic questionnaire and electronic algorithm. Usual care was as provided by the women's general practitioner according to their preferences.

Outcome measures: Before and after treatment, the women completed diaries (DRSP), the measure yourself concerns and well-being, and other questionnaires. Intention-to-treat (ITT) and per protocol (PP) analyses were performed.

Results: In Germany, the study could not proceed because of legal limitations. In Sweden, recruitment proved extremely difficult. In the Netherlands and Sweden, 60 women were randomized (UC + HT: 28; UC: 32), data of 47/46 women were analyzed (ITT/PP). After 4 months, relative mean change of DRSP scores in the UC + HT group was significantly better than in the UC group ($p = 0.03$).

Conclusions: With respect to recruitment and different legal status, it does not seem feasible to perform a larger, international, pragmatic randomized trial on (semi-)individualized homeopathy for PMS/PMDD. Since the added value of HT compared with UC was demonstrated by significant differences in symptom score changes, further studies are warranted.

Keywords: premenstrual, PMS/PMDD, homeopathy, randomized clinical trials, pragmatic trials

Introduction

Among women of reproductive age, severe premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are common (10%–30% and 1%–8%, respectively), with consequences for social life and work productivity.[1,2] Theories regarding biologic mechanisms underlying mood symptoms in PMDD remain unresolved as yet.[3] For severe symptoms, ovulation suppression or serotonin reuptake inhibitors are recommended.[4,5] However, in pharmacological

[1]Department of Health and Nutrition, Louis Bolk Institute, Bunnik, The Netherlands.
[2]Department of Nursing, Mid-Sweden University, Sundsvall, Sweden.
[3]Naturopathy and Integrative Medicine, Department of Gynecological Endocrinology and Reproductive Medicine, University Women's Hospital, Universitätsfrauenklinik Heidelberg, Heidelberg, Germany.

treatment, side effects could occur and many women prefer natural approaches.[4–6] For these women, homeopathy could be an option.

Background

In various uncontrolled studies and case series, beneficial effects of treatment with homeopathic medicines in women with PMS have been described.[7–9] In a randomized, controlled, double-blind pilot study and follow-up study, significant effects of homeopathic medicines compared with placebo were observed.[10,11] Therefore, it is important to further explore homeopathic treatment for women with PMS/PMDD. Our research group designed a semistandardized treatment plan with 11 homeopathic medicines.[8] In a feasibility study and extended observational study (2007–2011), the use of this treatment plan was evaluated as feasible.[8,12] A clinically relevant improvement of premenstrual symptoms (PMS scores decrease ≥50%) was measured after ≥8 months in 57.5% of the women.[12]

Methods

Objectives

The objectives of this study were as follows:

(1) To investigate the feasibility of organizing an international multicenter pragmatic trial on a (semi-) individualized homeopathic add-on treatment (usual care [UC] + HT, further referred as HT) compared with UC alone.
(2) To measure and compare effect sizes in both groups.

Design

This exploratory study was designed as a randomized controlled study with two parallel groups. Figure 1 shows the design flow chart.

It was planned to recruit women in the Netherlands, Germany, and Sweden. Interested women received oral and written information. If randomized to UC, they would be offered homeopathic treatment after the study. Women who signed for informed consent received an individual study number and completed diaries (daily record of severity of problems [DRSP]) to assess premenstrual symptoms for 2 months/cycles. Inclusion criteria were women aged 18–50 years and diagnosed as having PMS according to the International Classification for Primary Care (ICPC-2) or PMDD according to the Diagnostic Statistic Manual (DSM-IV) criteria based on prospective daily rating of symptoms during two complete menstrual cycles.[13,14] Exclusion criterion was major psychiatric comorbidity or physical comorbidity with large impact on general health.

Randomization

After confirmation of the diagnosis of PMS/PMDD, women were invited for an intake visit with the researcher in the Netherlands or a telephone meeting with the researcher in Sweden. The sequence of assignment to HT or UC was defined by a random allocation software program operated by an independent researcher at the Louis Bolk Institute. The actual sequence of allocation was defined by order of inclusion into the treatment phase of the study. The women were prestratified for severity of symptoms to ensure equal distribution in the two study groups: mild PMS and moderate to severe PMS and PMDD. Separate randomization lists were generated in blocks of six. The allocation was concealed to researchers and participants until the moment of disclosure, after the intake interview.

Procedures

Online self-report questionnaires were provided. Baseline measurements were taken during the screening phase and at the intake interview (T0), intermediate measurements after the second month/cycle (T2), and final measures after the fourth month/cycle (T4), see Figure 1. Furthermore, a researcher contacted each participant 1 and 3 months after the start of the intervention and after completion of the study.

Intervention

All women were to continue the care or treatment they were already receiving before the start of the study. Women in the HT group were to contact a homeopath who was a member of the Association of Scientific Homeopathy in Sweden or a homeopathic doctor who was a member of the Doctors Association for Integrative Medicine in the Netherlands. All had practical experience in individualized homeopathy for at least 5 years and were instructed on how to apply the treatment plan. Consultations were as usual, with detailed history, taking $\sim$1 h at the first visit and half an hour at follow-up visits. A semistandardized treatment plan for homeopathic medicine selection was used. It comprised a patient questionnaire with 123 items and a computerized algorithm to process the answers.[8] Study medication was provided by Deutsche Homoöpathische Union (Karlsruhe, Germany) and DCG Nordic (Göteborg, Sweden). At the first visit, the homeopaths were instructed to prescribe one of 11 preselected homeopathic medicines, according to the algorithm outcome. At follow-up visits, any other homeopathic medicine (in addition to these 11) could be prescribed.

Women in the UC group were to consult their own general practitioner (GP). Treatment could include advice about nutrition, lifestyle, conventional medicines, and other treatments, including referral to a gynecologist or psychiatrist. If women did not want to consult their GP, they were not obliged to do so under the study protocol.

In the Netherlands, homeopathic treatment is partly reimbursed if women have additional insurance, and in Sweden, it is not reimbursed at all. The study budget provided for covering nonreimbursed costs of homeopathic treatment.

Data collection and analysis

Outcome variables. Outcome variables for feasibility evaluation were time needed to recruit 90 women into the study, preferences for several treatment options, treatment expectations, adherence to the therapy, and numbers of complete records returned by patients, homeopaths, and GPs.

Effect sizes were calculated between measurements at baseline (T0) and after 4 months/menstrual cycles (T4). Primary outcome variables for the effect size calculation were differences between groups in mean change of DRSP

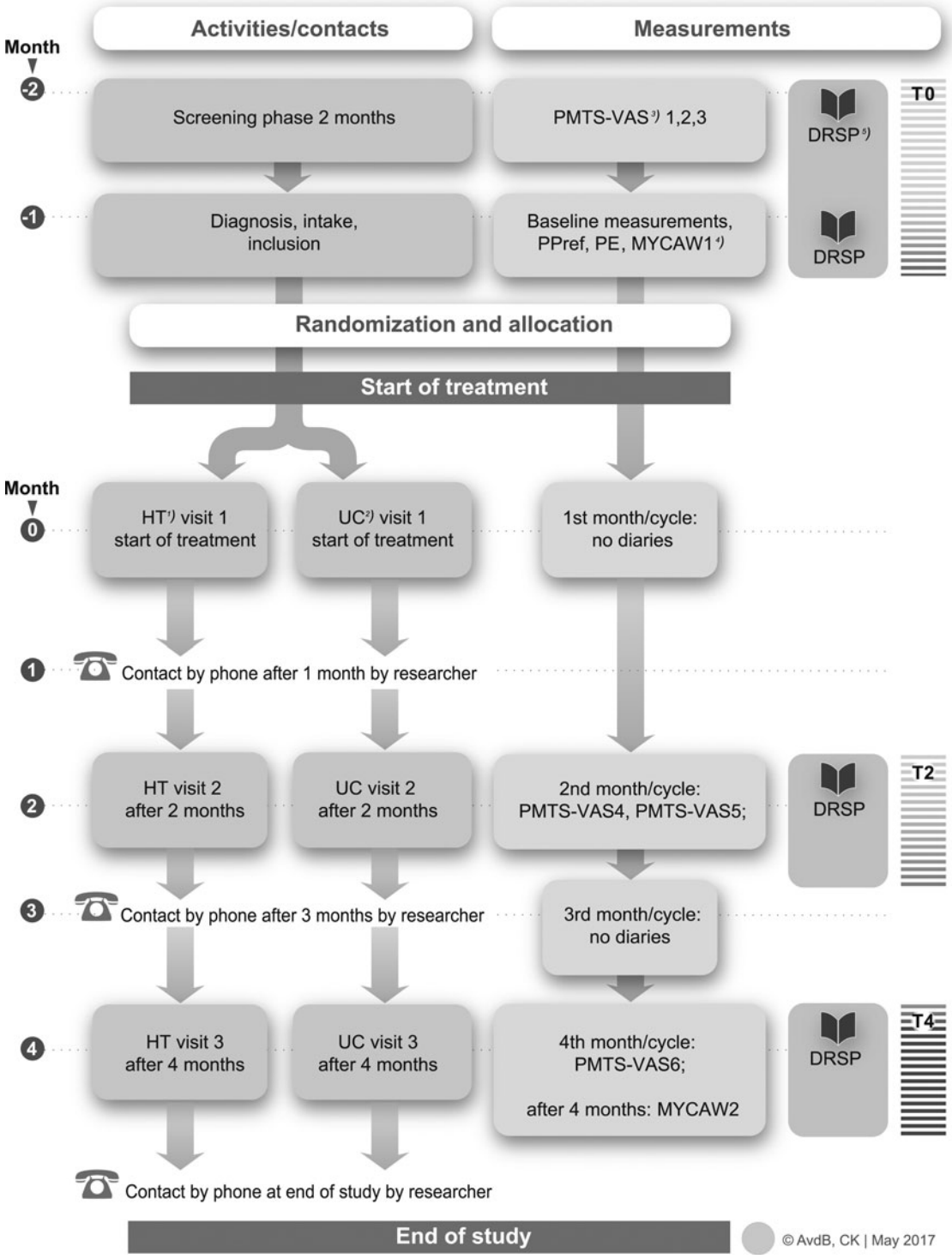

FIG. 1. Design flow chart. [1]HT, homeopathic add-on treatment; [2]UC, usual care; [3]PMTS-VAS, premenstrual tension syndrome visual analog scale; [4]PPref, PE, MYCAW, patient preferences, patient expectations, measure yourself concerns and well-being; [5]DRSP, daily record of severity of problems.

total scores. Secondary outcome variables were percentage of responders (≥50% decline in total DRSP scores), changes in the premenstrual tension syndrome self-rating visual analog scale (PMTS-VAS), and changes in main concern and well-being by the measure yourself concerns and well-being (MYCAW) questionnaire.

Another outcome variable was the number of reported adverse events (safety parameter).

Measurement instruments. See also Figure 1:

(1) DRSP was the primary outcome measure to evaluate change of premenstrual symptoms. It recorded 21

premenstrual symptoms as well as the impact on work productivity/school, social activities, and contacts, 24 items in total.[15] It was validated and recommended to quantify outcomes of PMS/PMDD research.[3,15]

(2) The PMTS-VAS rated 12 premenstrual symptoms (scale 0–100) and was completed during menstruation: three times before and three times during the intervention.[16,17]
(3) The women's first (and second) main burden/concern and perceived general health were measured by the MYCAW questionnaire (scale 0–6).[18]
(4) Preferences of the women for various treatment options were evaluated in the patient preference questionnaire (scale 1–6).[19]
(5) Patients' expectations were measured at baseline (scores 1–5 per item).

Statistical analyses

No previous studies with (semi-)individualized homeopathy versus standard care in women with PMS/PMDD have been performed. Therefore, it was difficult to estimate the sample size as necessary in a randomized study to detect significant differences between the groups. This pilot study aimed to include, in total, 90 women to be randomized in Sweden, the Netherlands, and Germany (45 in each group). Taking into account an estimated 25% dropout rate, the aim was to recruit 114 women, 38 in each country (19 HT, 19 UC).

Descriptive statistics were used for feasibility evaluation. DRSP score changes over time were calculated by subtracting the baseline score (T0) from the end score (T4) in both groups. The means of these changes were compared between both groups using *t*-tests (between-groups analysis). Effect sizes were expressed using Cohen's *d*, with the following interpretation: 0.8 = large, 0.5 = moderate, and 0.2 = small, practical significant effect.[20]

The percentage of responders was assessed by calculating the percentage of women with total DRSP score changes of ≥50% in both groups as this is regarded as a clinically relevant improvement.[21] The chi-square test was used to calculate differences between the groups, with $p \leq 0.05$ defined as a significant result (between-groups analysis).

MYCAW score changes over time were calculated by subtracting the T0 score from the T4 score in both groups. The means of these changes in both groups were compared using *t*-tests (between-groups analysis). Effect sizes were expressed using Cohen's *d*. Significance of the differences was determined using *t*-tests or Kruskal–Wallis rank-sum tests for non-normal distribution.[22]

For the PMTS-VAS, differences in changes between UC and HT groups between the last screening time point (T0) and the treatment time points (T2, T4) were tested for significance using *t*-tests.

Statistical analysis of baseline characteristics was performed on the full analysis set, including all randomized women. The analysis of differences in treatment preferences and confidence in treatment options was corrected for multiple testing by multiplying *p*-values with the number of tests. For the primary outcome measures regarding effect size calculation, intention-to-treat (ITT) analysis was performed, including all randomized women who had started the assigned treatment and completed at least one follow-up questionnaire. All other analyses were performed as per protocol (PP), including all women who had executed the intervention as described in the study protocol.

Ethical and legal considerations

The trial was registered at the Dutch trial register (http://trialregister.nl) on August 6, 2012, under number NTR3560. The study was conducted in accordance with regulations in the Netherlands and Sweden, the Declaration of Helsinki, and in adherence to the International Conference on Harmonisation guideline for Good Clinical Practice. In the Netherlands, the study was approved by the Medical Ethical Review Board at Tilburg (Metopp) on May 14, 2012 (Nr. NL3908702812). In Sweden, ethical approval was granted by the Central Ethical Review Board in Stockholm (Dnr Ö 46-2012) in December 2012.

In Germany, legal issues proved insuperable. After correspondence with the Ethics Committee of the Medical Faculty at Heidelberg, the study was transformed into a nonrandomized case series. However, on May 19, 2015, the study protocol was classified as a drug trial by German authorities (Bundesinstitut für Arzneimittel und Medizinprodukte, Regierungspräsidium Karlsruhe) and approval was not granted. At that time point, parallel studies in the Netherlands and Sweden were almost finished. No further time was invested to get the study started in Germany. It did not seem feasible to adapt the ethics application into an application for a drug trial since in the study protocol, homeopaths were allowed to prescribe any homeopathic medicine out of a selection of more than a thousand, including the 11 that were included in the algorithm.

Results

In the Netherlands, recruitment started in October 2012. In October 2014, the target number of 38 included women was achieved. Recruitment in Sweden started in April 2013, but was hampered because of controversies about performing research on homeopathy at a Swedish university. Many women who showed interest did not proceed or dropped out after randomization. In spring 2016, further recruitment was stopped, 22 Swedish women were included.

Altogether, 244 women were interested, 96 started diaries in the screening phase, 60 were included and randomized, 54 started the treatment phase, and 47 had at least one response measurement. ITT analysis was performed on 47 women (HT: 24, UC: 23) and PP analysis on 46 women (HT: 24, UC: 22). A CONSORT flow chart is given in Figure 2.

During the treatment phase, 89.4% diaries (DRSP) were completed as planned.

Baseline characteristics

Baseline characteristics of all 60 randomized women are presented in Table 1. Preference for homeopathy was significantly higher in the UC group than in the HT group ($p < 0.001$). In the analyzed group ($N = 46$), there was no significant difference in preference for homeopathy between the groups.

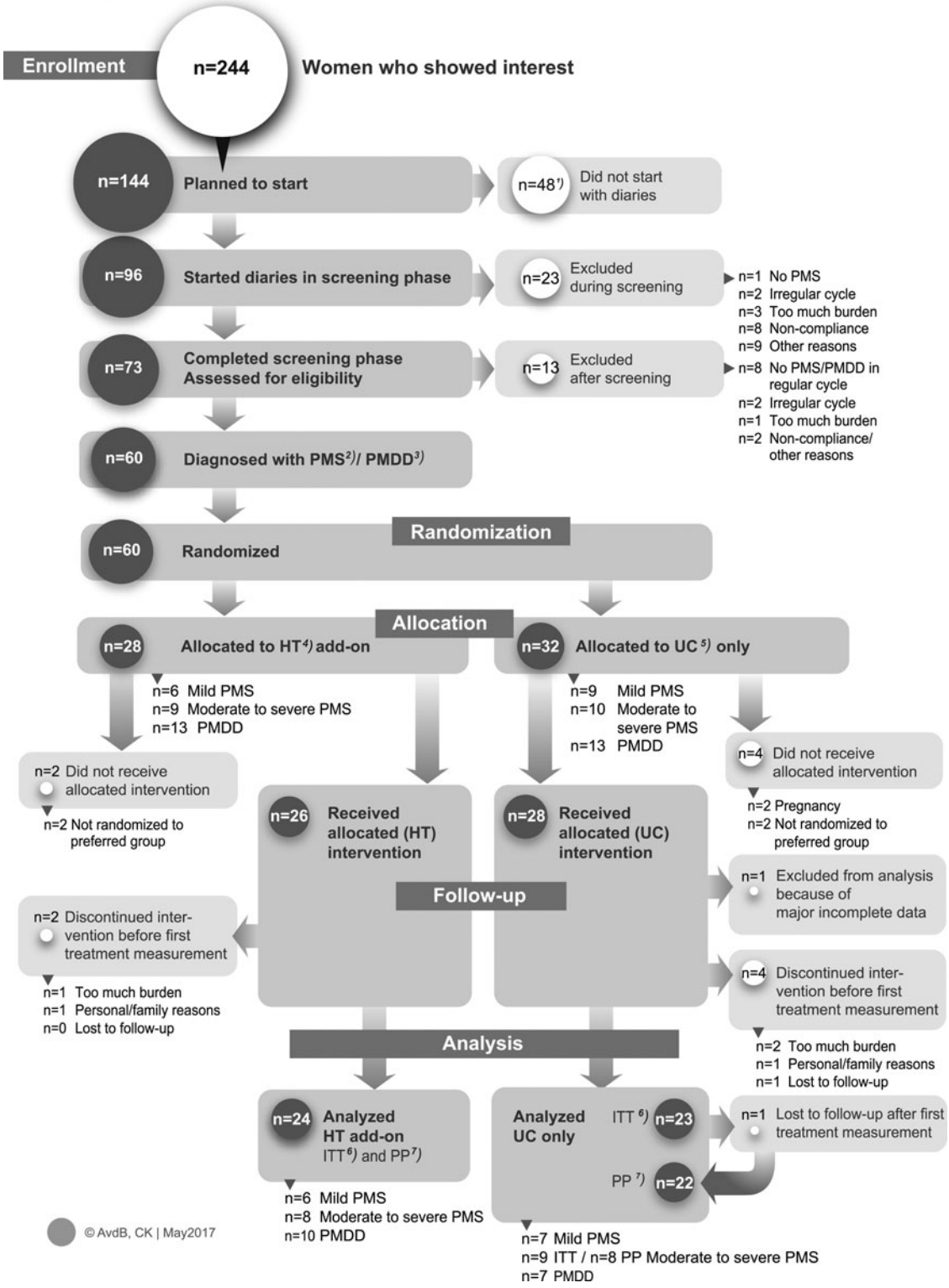

FIG. 2. CONSORT flow chart. [1]The reasons for not starting with diaries were not always known, some women did not react to e-mails or calls. Most reported reasons were as follows: too busy, the diaries would be too much of a burden, or they wanted immediate treatment and could not wait for 2 months; [2]PMS, premenstrual syndrome; [3]PMDD, premenstrual dysphoric disorder; [4]HT, homeopathic add-on treatment; [5]UC, usual care; [6]ITT, analysis by intention-to-treat; [7]PP, analysis per protocol.

Table 1. Baseline Characteristics, Preferences, and Expectations of Women in the Study, Full Analysis Set

Baseline characteristics	*Usual care (UC)* N = *32*	*Homeopathy (HT)* N = *28*	p-*Values**
Biometrical and gynecological features			
Age (years ± standard deviation [SD])	37.7 (±5.5)	38.9 (±5.5)	
Body mass index (BMI ± SD)	24.3 (±4.6)	24.3 (±4.2)	
Mean age of first menarche (years ± SD)	13.3 (±1.9)	12.7 (±1.5)	
Mean number of pregnancies (*N* ± SD)	1.7 (±1.3)	1.6 (±1.4)	
Mean number of births (*N* ± SD)	1.2 (±1.2)	1.3 (±1.1)	
Mean duration of premenstrual syndrome (PMS) in years (years ± SD)	2.9 (±0.3)	2.9 (±0.4)	
Gynecological and psychiatric history			
Past gynecological treatment (*N* [%])	16 (50.0%)	10 (35.7%)	
Past hormonal treatment (*N* [%])	14 (43.8%)	9 (32.1%)	
Previous PMS treatment (*N* [%])	22 (68.8%)	18 (64.3%)	
History of postpartum depression (*N* [%])	2 (6.3%)	3 (10.7%)	
History of depression (*N* [%])	17 (53.1%)	16 (57.1%)	
Other psychiatric history (*N* [%])	8 (25.0%)	7 (25.0%)	
Actual usual care for premenstrual disorders (PMD), reported at intake			
Antidepressants (*N* [%])	2 (6.3%)	1 (3.6%)	
Oral contraceptive pill (OCP) (*N* [%])	1 (3.1%)	2 (7.1%)	
Homeopathic medicines (all types) (*N* [%])	0 (0.0%)	1 (3.6%)	
Herbal medicines (*N* [%])	5 (15.6%)	4 (14.3%)	
Vitamins/supplements (*N* [%])	14 (43.8%)	12 (42.9%)	
Psychological interventions (*N* [%])	2 (6.3%)	1 (3.6%)	
Exercise, including sports (*N* [%])	15 (46.9%)	9 (32.1%)	
Relaxation therapy, including yoga (*N* [%])	7 (21.9%)	5 (17.9%)	
Dietary measures (*N* [%])	15 (46.9%)	8 (28.6%)	
Painkillers (*N* [%])	2 (6.3%)	2 (7.1%)	
Other measures/treatments (*N* [%])	3 (9.4%)	1 (3.6%)	
PMD treatment preferences[a]			
Preference for antidepressants (*N* [%])	2 (6%)	3 (11%)	0.011
Objections to antidepressants (*N* [%])	27 (84%)	18 (64%)	
Preference for OCP (*N* [%])	2 (6%)	1 (4%)	
Objections to OCP (*N* [%])	26 (81%)	23 (82%)	
Preference for homeopathic treatment (*N* [%])	30 (94%)	29 (71%)	<0.001
Objections to homeopathic treatment (*N* [%])	0 (0%)	0 (0%)	
Preference for herbal medicines (*N* [%])	25 (78%)	18 (64%)	
Preference for vitamins/supplements (*N* [%])	27 (84%)	16 (57%)	
Preference for cognitive behavioral therapy (*N* [%])	20 (63%)	14 (50%)	0.012
Preference for exercise (*N* [%])	26 (82%)	20 (71%)	
Preference for relaxation therapy (*N* [%])	25 (78%)	18 (64%)	
Confidence in treatment options[b]			
Conventional medicine (*N* [%])	8 (25%)	6 (21%)	<0.001
Homeopathic treatment (*N* [%])	19 (59%)	10 (36%)	
Positive treatment expectations[c]			
Conventional medicine (N [%])	10 (31%)	4 (14%)	
Homeopathic treatment (N [%])	21 (66%)	13 (46%)	
Daily record of severity of problems (DRSP) total scores (mean in premenstrual week ± SD)	457 (±167)	442 (±162)	

*Differences between the UC and HT groups were tested using *t*-tests for numerical variables and chi-square tests for frequency variables.

[a]PMD treatment preferences were measured by the Preferences questionnaire (PPref). Preference was defined by some preference + strong preference. Objection was defined by objection + strong objection.

[b]Confidence in treatment was measured by the first Expectations questionnaire (PE1). Confidence in treatment options was defined by very effective + effective.

[c]Treatment expectations were measured by the first Expectations questionnaire (PE1). Positive expectation was defined by major improvement + cure.

UC, usual care; HT, homeopathic add-on treatment; SD, standard deviation.

Table 2. Homeopathic Medicines Prescribed During the Study in the Group with Additional Homeopathic Treatment

N = *24*	N *(%)*
First prescribed homeopathic medicine[a]	
Sepia officinalis	11 (45.9%)
Natrium muriaticum	8 (33.3%)
Cimicifuga racemosa	1 (4.2%)
Lachesis mutus	1 (4.2%)
Lilium tigrinum	1 (4.2%)
Phosphorus	1 (4.2%)
Pulsatilla pratensis	1 (4.2%)

Homeopathic potencies used Q-potencies (Q: 1:50,000), D30, D200 (D: decimal 1:10), 30 CH (C: centesimal 1:100), 30K, 200K, and MK (K: Korsakov, 1:100), globules or droplets.

[a]In six women, the prescription was changed during the study; in five, these prescriptions were also algorithm based; in one woman, it was not.

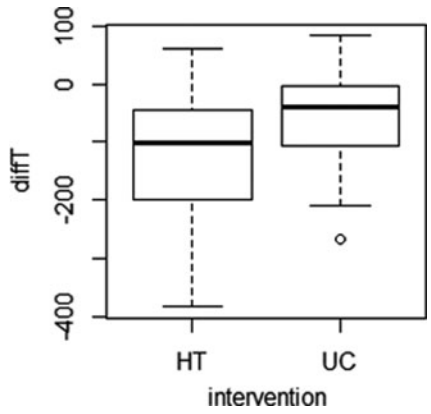

FIG. 3. Box plot of the DRSP total score change between baseline (T0) and 4 months (T4) for the UC and HT groups ($N = 46$).

Interventions

In both groups, usual care before the study was continued throughout the study, for example, oral contraceptive pills (OCPs), antidepressants, Levonorgestrel-releasing intrauterine system (IUS), supplements, or relaxation. Additionally, in the UC group, 10 of 22 women consulted their GP in the context of usual care only in the study. Of these, five followed up the GP's advice: OCP, IUS, referrals to a gynecologist, psychosomatic psychotherapist, and osteopath. Other women in the UC group chose not to visit their GP because they had already tried several options in the past (such as OCPs or antidepressants) and suffered from side effects or did not have confidence in conventional treatment options.

All 24 women in the HT group visited the homeopath they were assigned to in addition to the usual care they were already receiving. All treating homeopaths, eleven in the Netherlands and five in Sweden, worked in private practices and adhered to the homeopathic treatment plan. Homeopathic medicines prescribed are presented in Table 2. In the HT group, one woman started and another stopped taking antidepressants.

Outcome measures

The comparison of DRSP response differences between the groups is presented in Table 3. The changes in DRSP total scores ($p = 0.03$) were significantly different in favor of the HT group (PP and ITT). Cohen's effect size value ($d = 0.62$) suggested a moderate to high practical significance. A box plot of the DRSP total score changes is given in Figure 3; DRSP changes over time in Figure 4.

In the HT group, 10 women (41.7%) were identified as positive responders, and in the UC group, four were identified (18.2%). The difference between the groups was not significant (chi-square test, $p = 0.08$).

Changes of first main burden/concern scores were significantly different between the groups in favor of the HT group (*t*-test; $p = 0.03$), with moderate to high practical significance ($d = 0.67$), see Table 3. Changes in perceived

Table 3. Comparison Between Usual Care Alone and Homeopathic Add-On Therapy for Difference in Changes of Daily Record of Severity of Problems Total Scores and Measure Yourself Concerns and Well-Being Scores, Between Baseline (T0) and Endpoint (T4)

N = *46*	*T0 mean UC (±SD)*	*T0 mean HT (±SD)*	*T4 mean UC (±SD)*	*T4 mean HT (±SD)*	*T0–T4 mean change difference (CI)*	*Cohen's* d *(CI)*	*Student t-test* p
DRSP total scores (score range: 168–1008)	468 (±177)	429 (±166)	414 (±163)	289 (±126)	−75 (−143 to −6.31)	0.69 (0.03–1.30)	0.033
MYCAW first main burden/ concern (score 0–6)	4.82 (±0.85)	5.21 (±0.66)	3.86 (±1.70)	3.00 (±1.59)	−1.26 (0.14–2.37)	0.67 (0.04–1.29)	0.028
MYCAW perceived general health (score 0–6)	2.50 (±1.47)	2.96 (±1.43)	2.91 (±1.27)	2.33 (±1.34)	−1.03 (0.12–1.95)	0.68 (0.05–1.30)	0.028

Data are given as mean with CI.

CI, confidence interval; DRSP, daily record of severity of problems; MYCAW, measure yourself concerns and well-being.

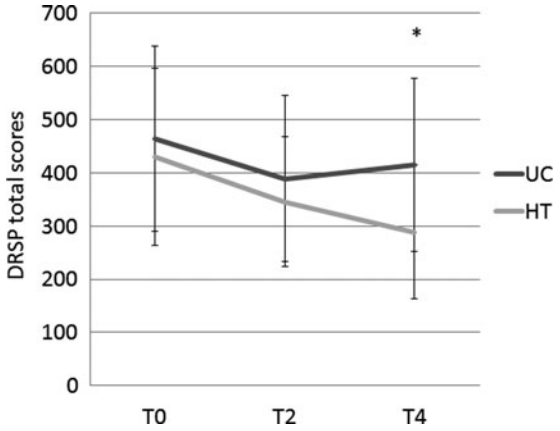

FIG. 4. DRSP total scores over time. *At T4, the difference between UC and HT groups is significant ($p = 0.007$). DRSP (premenstrual symptom diaries); T0, baseline; T2, treatment phase after 2 months; T4, treatment phase after 4 months.

general health were also significantly different in favor of the HT group (*t*-test; $p = 0.03$), with moderate to high practical significance ($d = 0.68$).

For changes of the mean sum of 12 VAS item scores over time, a significant decrease was identified only in the HT group for the interval T0–T2 (within-group analysis; $p = 0.04$).

Side effects and aggravations

In Table 4, reported possible aggravations after taking homeopathic medicines and side effects of conventional treatment are summarized.

Discussion

This study indicates that it does not seem feasible to perform a larger international trial of similar design to study the added value of a (semi-)individualized homeopathic treatment in women with PMS/PMDD. Major obstacles were identified in the present study, such as academic opposition in Sweden and different legislation in Germany.

Different legal statuses of homeopathy, homeopathic professionals, and homeopathic products between countries have to be considered before starting a study on homeopathy.[23,24] During the present study, it became clear that it was not possible to perform this pragmatic trial in Germany. The German Medicines Act discriminates drugs from particular therapeutic systems, such as homeopathy,[25] whereas, for example, in Canada, homeopathic medicines are classified as natural health products. Canadian pragmatic studies with individually prescribed homeopathic medicines were conducted in accordance with the Natural and Non-prescription Health Products Directorate (D. Brulé, personal communication, July 2017).[26] In the United Kingdom, a clinical trials authorization of the Medicines Health Regulatory Authority was not required for pragmatic trials with individually prescribed homeopathic medicines on menopausal problems and depression.[27,28] These countries may therefore be taken into consideration for future international studies on this topic.

Previous research has demonstrated that homeopathy can reduce costs in primary healthcare.[29] Further study could explore if this also accounts for women with PMS/PMDD.

Homeopathy is often used alongside usual care.[30] Therefore, a pragmatic study design was chosen to more closely resemble everyday practice and measure benefits of specific treatment procedures in routine clinical practice.[31,32] The homeopathic treatment was evaluated as a whole: consultation plus homeopathic medicine. This has consequences for interpretation of results. A therapeutic relationship with attention for personal needs, emotional support, and offering possible solutions (as in individualized homeopathic treatment) can have an important nonspecific effect.[33,34] It is therefore likely that part of the effect of individualized homeopathic treatment is due to a context effect. In response to a pilot study in the United Kingdom on patients with rheumatoid arthritis, experts commented that it was not possible to make conclusions about the relative effects of the consultation or the remedy itself. Clearly, more research is needed.[35,36]

Regarding the PMS symptom scores, significant differences in favor of the HT group were found, with high practical significance. These findings indicate that this homeopathic treatment has added value compared with UC in women with PMS/PMDD. In the HT group, reduction of premenstrual symptoms, alleviation of first main burden/

Table 4. Reported Possible Major Aggravations of Homeopathic Medicines and Side Effects of Conventional Treatment During the Study

Group	*Treatment*	*Symptoms*
UC	Levonorgestrel-releasing intrauterine system (IUS)	Constant bleeding
HT[a]	Sepia officinalis 30K	Feeling depressed, with severe symptoms during a period of 4 days
	Sepia officinalis LM6	Restlessness, negative thoughts during a period of 1–2 weeks
	Sepia officinalis D30	Lumps in breasts, urinary tract infection, stomach pain
	Sepia officinalis D30	More pain and anxiety, aggravation of skin problems
	Sepia officinalis C200	More emotional instability, depressed

Five other women in the HT group reported temporarily minor aggravations: more quarrelsome, short period with nausea and palpitation, intermittent bleeding and abdominal pain, more emotional, and worsening of general symptoms.

[a]Of the five women in the HT group with reported major aggravations, four remained in the study, one dropped out; the homeopathic medicine was stopped in four women, one continued homeopathic treatment; one woman started antidepressants and felt dull during a period of 1–2 weeks.

concern, and improvement of perceived general health were significantly better than in the UC group. Relatively more women in the HT group were identified as positive responders, although the difference between the groups was not statistically significant.

High outcome expectations could positively influence treatment results, as was found in acupuncture trials.[19] However, since women in the UC group had higher expectations of both conventional and homeopathic treatments than women in the HT group, it is unlikely that the differences in PMS symptom scores were due to expectation bias.

The pragmatic study design does not allow conclusions about efficacy of homeopathic medicines. To strengthen the body of evidence, replication of placebo-controlled as well as pragmatic trials on PMS/PMDD and homeopathy is recommended. Considering the promising outcomes, this specific homeopathic treatment could be implemented in primary care as an additional option for women with PMS/PMDD who are interested in homeopathy.

Conclusions

It was not feasible to conduct a pragmatic international trial of homeopathy in these three countries. Since the added value of HT compared with UC was demonstrated by significant differences in symptom score changes, repetition of placebo-controlled as well as pragmatic studies in this field is recommended.

Trial Reporting Guidelines

The reporting of this trial is according to the updated guidelines of the Consolidated Standards of Reporting Trials (CONSORT), its extensions for pragmatic trials, and for trials in homeopathic treatment (RedHot).

Acknowledgments

The authors thank Inge Boers and other personnel of the Louis Bolk Institute for practical and administrative support, Lennard Klein for technical support, and Annet van den Berg for the infographics. This work was supported by a grant from the International Scientific Committee for Homeopathic Investigations (ISCHI), the Swedish Scientific Homeopathic Association, the Hilly de Roever Bonnet Fund, and the Royal Dutch consumers association for homeopathy (KVHN). The foundations that financed this study as well as the companies that provided the study medication were not involved in interference of any kind with the performance, analysis, or writing of study results.

Author Disclosure Statement

No competing financial interests exist.

References

1. Halbreich U, Borenstein J, Pearlstein T, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). Psychoneuroendocrinology 2003;28 Suppl 3:1–23.
2. Heinemann LA, Minh TD, Filonenko A, Uhl-Hochgraber K. Explorative evaluation of the impact of severe premenstrual disorders on work absenteeism and productivity. Womens Health Issues 2010;20:58–65.
3. O'Brien PM, Backstrom T, Brown C, et al. Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: The ISPMD Montreal consensus. Arch Womens Ment Health 2011;14:13–21.
4. O'Brien S, Rapkin A, Dennerstein L, Nevatte T. Diagnosis and management of premenstrual disorders. BMJ 2011;342:d2994.
5. Jarvis CI, Lynch AM, Morin AK. Management strategies for premenstrual syndrome/premenstrual dysphoric disorder. Ann Pharmacother 2008;42:967–978.
6. Sundstrom-Poromaa I, Bixo M, Bjorn I, Nordh O. Compliance to antidepressant drug therapy for treatment of premenstrual syndrome. J Psychosom Obstet Gynaecol 2000;21:205–211.
7. Komar T, Peck KS, Torline JR, Deroukakis M. A qualitative study to determine the efficacy of the homeopathic simillimum in the treatment of premenstrual syndrome. Am J Hom Med 2006;99:196–204.
8. Klein-Laansma CT, Jansen JCH, van Tilborgh AJW, et al. Semi-standardised homeopathic treatment of premenstrual syndrome with a limited number of medicines: Feasibility study. Homeopathy 2010;99:192–204.
9. Danno K, Colas A, Terzan L, Bordet MF. Homeopathic treatment of premenstrual syndrome: A case series. Homeopathy 2013;102:59–65.
10. Yakir M, Kreitler S, Brzezinski A, et al. Effects of homeopathic treatment in women with premenstrual syndrome: A pilot study. Br Homoeopath J 2001;90:148–153.
11. Yakir, M. Evaluating homeopathic medicine: Clinical and social research with pre-menstrual syndrome (PMS) as a case study. PhD Thesis, English version. Hebrew University Jerusalem, Israel, October 2002.
12. Klein-Laansma CT, Jansen JCH, Van Tilborgh AJW, Van Vliet M. Evaluation of semi standardized individualized homeopathic treatment of 77 women with premenstrual disorders: Observational study with 9 months follow-up. Altern Integr Med 2014;3:164.
13. WONCA International Classification Committee. ICPC-2: International Classification of Primary Care. Second edition. Oxford, United Kingdom: Oxford University Press, 1998.
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth edition. Washington, DC: American Psychiatric Association, 1994.
15. Endicott J, Nee J, Harrison W. Daily Record of severity of problems (DRSP): Reliability and validity. Arch Womens Ment Health 2006;9:41–49.
16. Steiner M, Peer M, Macdougall M, Haskett R. The premenstrual tension syndrome rating scales: An updated version. J Affect Disord 2011;135:82–88.
17. Steiner M, Streiner DL. Validation of a revised visual analog scale for premenstrual mood symptoms: Results from prospective and retrospective trials. Can J Psychiatry 2005;50:327–332.
18. Paterson C, Thomas K, Manasse A, et al. Measure yourself concerns and wellbeing (MYCaW): An individualised questionnaire for evaluating outcome in cancer support care that includes complementary therapies. Complement Ther Med 2007;15:38–45.
19. Linde K, Witt CM, Streng A, et al. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. Pain 2007;128:264–271.

20. Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences. Second edition. New York: Academic Press.
21. Borenstein JE, Dean BB, Leifke E, et al. Differences in symptom scores and health outcomes in premenstrual syndrome. J Womens Health 2007;16:1139–1144.
22. Hollander M, Wolfe DA. Nonparametric Statistical Methods. New York: John Wiley and Sons, 1973:115–120.
23. Fønnebø V, Kristiansen T, Falkenberg T, et al. Legal status and regulation of CAM in Europe Part II—herbal and homeopathic medicinal products, 2012 [homepage on the Internet]. Online document at: https://phaidra.univie.ac.at/view/o:291682, accessed January 12, 2018.
24. Wiesener S, Falkenberg T, Hegyi G, et al. Legal status and regulation of CAM in Europe. Part I—CAM regulations in the European countries [homepage on the Internet]. Online document at: https://phaidra.univie.ac.at/view/o:291583, accessed January 12, 2018.
25. BfArM. German medicines act (AMG), last updated 2016, § 25 [homepage on the Internet]. Online document at: https://bfarm.de/EN/Drugs/licensing/zulassungsarten/pts/_node.html;jsessionid=ACD58249C1C032AB1BCEDC45D3CBFCC3.1_cid319, accessed January 10, 2018.
26. Natural and Non-prescription Health Products Directorate (NNHPD). Natural health products regulations, 2004. Online document at: https://canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/regulation.html, accessed January 12, 2018.
27. Relton, C. A new design for pragmatic randomised controlled trials: A 'patient cohort' RCT of treatment by a homeopath for menopausal hot flushes. School of Health and Related Research, University of Sheffield. PhD Thesis, April 2009.
28. Viksveen P, Relton C, Nicholl J. Benefits and challenges of using the cohort multiple randomised controlled trial design for testing an intervention for depression. Trials 2017;18:308.
29. Baars EW, Kooreman P. A 6-year comparative economic evaluation of healthcare costs and mortality rates of Dutch patients from conventional and CAM GPs. BMJ Open 2014;4:e005332. Erratum in: BMJ Open. 2014;4:e005332corr1.
30. Domoney CL, Vashisht A, Studd JW. Use of complementary therapies by women attending a specialist premenstrual syndrome clinic. Gynecol Endocrinol 2003;17:13–18.
31. Roland M, Torgerson DJ. Understanding controlled trials: What are pragmatic trials? BMJ 1998;316:285.
32. Porzsolt F, Rocha NG, Toledo-Arruda AC, et al. Efficacy and effectiveness trials have different goals, use different tools, and generate different messages. Pragmat Obs Res 2015;6:47–54.
33. Di Blasi Z, Harkness E, Ernst E, et al. Influence of context effects on health outcomes: A systematic review. Lancet 2001; 357:757–762.
34. Bensing JM, Verheul W. The silent healer: The role of communication in placebo effects. Patient Educ Couns 2010; 80:293–299.
35. Brien SB, Leydon GM, Lewith G. Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: A randomized controlled clinical trial. Rheumatology (Oxford) 2011;50:1070–1082.
36. Chatfield K, Mathie RT, Fisher P. Comment 2 on: Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: A randomized controlled clinical trial. Rheumatology (Oxford) 2011;50:1529–1531.

Address correspondence to:
Christien T. Klein-Laansma, MD
Department of Health and Nutrition
Louis Bolk Institute
Kosterijland 3-5
Bunnik 3981 AJ
The Netherlands

E-mail: ctlaansma@planet.nl