The treatment of premenstrual syndrome with preparations of *Vitex agnus castus*: a systematic review and meta-analysis

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BACKGROUND: Premenstrual syndrome is characterized by the cyclic occurrence of physical, behavioral and psychological symptoms during the luteal phase of the menstrual cycle disappearing within a few days of the onset of menstruation. Generally symptoms are mild, but 5—8% of women suffer from severe PMS. Apart from conventional drugs, like serotonin reuptake inhibitors and oral contraceptives, complementary and alternative medicines such as *Vitex agnus castus* are used by many women experiencing PMS.

OBJECTIVE: Our objective was to determine the efficacy, tolerability, and acceptability of *Vitex agnus castus* preparations for treatment of premenstrual syndrome.

STUDY DESIGN: All journals in the Ovid software from inception through January 2016 were searched, including the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO. Gray literature was searched by Google Scholar and manufacturers of *Vitex agnus castus* preparations were contacted for information about unpublished trials. We included randomized controlled trials with *Vitex agnus castus* in women with premenstrual syndrome and/or premenstrual dysphoric disorder with a minimal duration of 2 menstrual cycles. The eligibility of the manuscripts was assessed by 2 reviewers independently. The data abstracted included characteristics of the study design, characteristics of the patient population, intervention details, type of comparator, method of diagnosis, and outcome measures. We adhered to the PRISMA guidelines.

RESULTS: We found 17 randomized controlled trials of *Vitex agnus castus* in the treatment of premenstrual syndrome. Fourteen of these could be included in the quantitative analysis. Thirteen of 14 studies with placebo, dietary supplements, or herbal preparations as controls reported positive effects of *Vitex agnus castus* on total premenstrual syndrome symptoms. Unfortunately most of the trials are associated with a high risk of bias. The pooled effect of *Vitex agnus castus* in placebo-controlled trials was large (Hedges g, −1.21; 95% confidence interval, −1.53 to −0.88), but heterogeneity was extremely high (I^2, 91%). We were unable to single out factors that could explain this heterogeneity satisfactorily. The funnel plot and Egger tests suggest the presence of publication bias.

CONCLUSION: Although meta-analysis shows a large pooled effect of *Vitex agnus castus* in placebo-controlled trials, the high risk of bias, high heterogeneity, and risk of publication bias of the included studies preclude a definitive conclusion. The pooled treatment effects should be viewed as merely explorative and, at best, overestimating the real treatment effect of *Vitex agnus castus* for premenstrual syndrome symptoms. There is a clear need for high-quality trials of appropriate size examining the effect of standardized extracts of *Vitex agnus castus* in comparison to placebo, selective serotonin reuptake inhibitors, and oral contraceptives to establish relative efficacy.

Key words: meta-analysis, premenstrual syndrome, systematic review, *Vitex agnus castus*

Introduction

Premenstrual syndrome (PMS) is characterized by the cyclic occurrence of physical, behavioral, and psychological symptoms during the luteal phase of the menstrual cycle disappearing within a few days of the onset of menstruation.[1] Most women of reproductive age have ≥1 emotional or physical symptoms in the premenstrual phase of the menstrual cycle. Generally symptoms are mild, but 5-8% of women experience severe PMS: most of these women also meet the criteria for premenstrual dysphoric disorder (PMDD).[2] The main physical symptoms associated with PMS and PMDD are dizziness, palpitations, headache, edema, mastalgia, and abdominal pains. The main psychological symptoms are anxiety, depressive feelings, agitation, and aggression.[3] PMDD affects a subgroup of women and meets more stringent diagnostic criteria: (a) the presence of at least 5 of 11 luteal phase symptoms, one of which must be a mood symptom and symptoms must have begun to remit within a few days of the onset of

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Author Saskia Verkaik began the work on this review when she was in between jobs, and is currently employed by Acerta Pharma B.V., a biotechnology company not active in the field of premenstrual syndrome. The company had no involvement in any part of this study. The other three authors of the review have no potential conflicts to disclose.

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menstruation; (b) the symptoms must be severe enough to interfere significantly with social, occupational, sexual, or scholastic functioning; (c) the symptoms must be related to the menstrual cycle and must not be an exacerbation of another psychiatric condition; and (d) the criteria a, b, and c must be confirmed by prospective daily ratings.[4] Since a proportion of patients with severe PMS will not fulfill the stringent criteria of PMDD, the International Society for Premenstrual Disorders defined criteria for diagnosing the core premenstrual disorder. These criteria do not require a number of specific symptoms to be present. A single symptom causing substantial impairment suffices to meet the criteria for the diagnosis of the core premenstrual disorder.[1]

Hypotheses about the causes of PMS and PMDD include endocrine factors such as hypoglycemia, hyperprolactinemia, fluctuations in the levels of circulating estradiol and progesterone, and excessive amounts of aldosterone or antidiuretic hormone or lower nocturnal melatonin concentrations. Other hypotheses include neurotransmitters involvement, eg, serotonin and γ-aminobutyric acid. None of these hypotheses has been scientifically proven.[2,5-7] However, it is clear that without ovarian activity there is no PMS. This is the case in prepubertal or menopausal females, after bilateral ovariectomy or treatment with gonadotropin-releasing hormone analogs. Recently, a study showed abnormalities of the dorsolateral prefrontal function in women with PMDD.[8] The dorsolateral prefrontal cortex is a known target for gonadal hormones such as estrogen in nonhuman primates.[9,10] More than 80 different therapies have been suggested for the treatment of PMS/PMDD, resulting in conflicting information and many unsubstantiated claims of efficacy.[5] No single intervention is effective for all women. Moreover, there is a large placebo effect in the treatment of PMS. Of PMS patients, 20% experience an improvement in symptoms after 4 months of treatment with placebo.[11] No effective treatment for PMS is registered in Europe.[12,13] The US Food and Drug Administration has approved several selective serotonin reuptake inhibitors (SSRIs) for the treatment of PMDD. Professional guidelines advise a step-by-step approach to the treatment of PMS, starting with lifestyle and diet changes, the use of dietary supplements, and cognitive behavioral therapy.[5,13] The Royal College of Obstetricians and Gynecologists recommends SSRIs and drospirenone-containing combined oral contraceptives as first-line pharmaceutical interventions. Gonadotropin-releasing hormone analogs are also highly effective in treating severe PMS, but due to their effect on bone mineral density they should only be considered for severe cases that do not respond to SSRIs or combined oral contraceptives.[13] Nowadays SSRIs are the most prescribed first-line therapy in the treatment of severe PMS or PMDD with an effect size of −0.53 (95% confidence interval [CI], −0.83 to −0.23) and −0.51 (95% CI, −0.66 to −0.35), respectively.[14] SSRIs may cause side effects such as nausea, headache, anxiety, insomnia, sexual dysfunction, weight gain, anorexia,[3] or intestinal and gynecological bleeding.[15]

Apart from these conventional drugs and interventions, complementary and alternative medicines such as ginkgo, saffron, St John wort, evening primrose oil, soy, and *Vitex agnus castus* (*VAC*) are used by many women experiencing PMS.[16] The Association of Reproductive Health Professionals recommends *VAC* for treatment of mild PMS.[5] *VAC* is a small tree or shrub, widely distributed in the Mediterranean region of Europe and in Central Asia.[17] The parts used for medicinal purposes are the ripe dried fruits and extracts/concentrates of this part of the plant. Its constituents are flavonoids (casticin, isovitexin, orientin), iridoids (aucubin, agnuside, eurostide),

FIGURE 1
PRISMA 2009 flow diagram of included and excluded studies

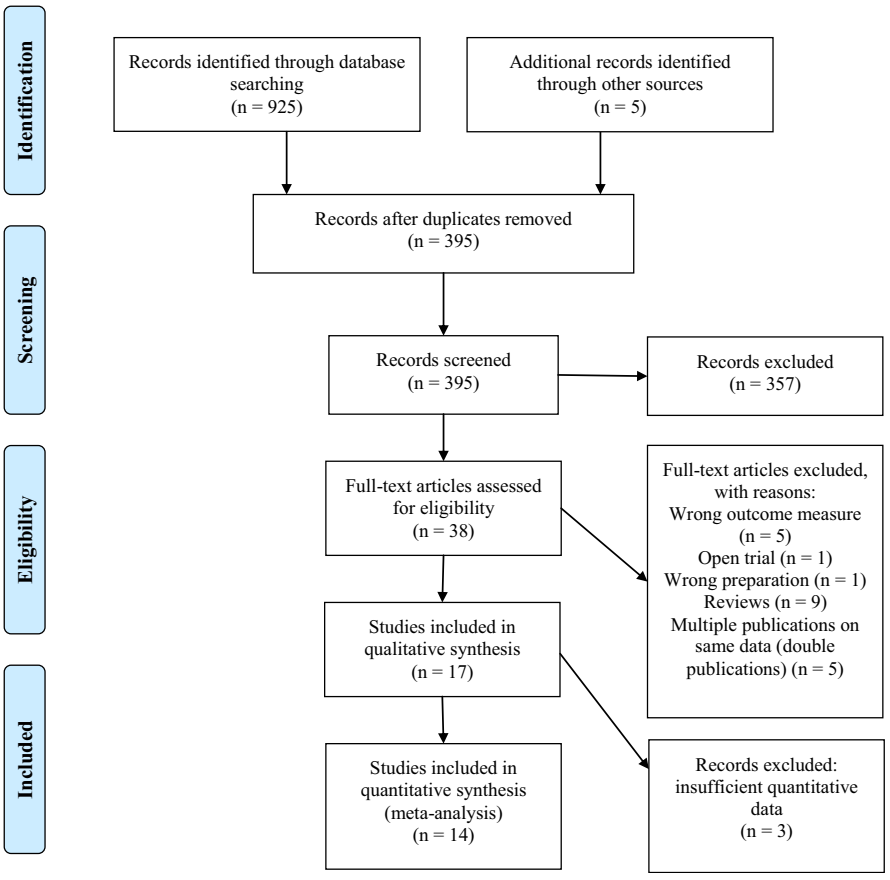

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TABLE 1
Characteristics of included studies in alphabetical order (N = 17)

Study	Study design	Patients	Intervention details	Comparator	Method of diagnosis	Outcome measures	Results
Atmaca et al,[37] 2003[a]	Single-blind	N = 41, mean age 33 y	*VAC* (Agnucaston [Bionorica, Neumarkt, Germany[b]]) or fluoxetine; dose range was 20–40 mg/d in both groups with flexible dosing, 3 menstrual cycles	Fluoxetine	DSM-IV	DSR, HAM-D, CGI-SI	No significant difference between intervention and control group on all outcome measures ($P > .05$)
Ciotta et al,[38] 2011	Double-blind	N = 57, reproductive age	*VAC* (extract (6–12:1; 20 mg/d) (corresponding to 180 mg/d plant material) or fluoxetine 20–40 mg/d, 2 menstrual cycles	Fluoxetine	DSM-IV	4 Items of HAM-D	Significantly greater decrease on 4 items on HAM-D in control group compared to intervention group ($P < .05$); in intervention group significant decrease on 4 items on HAM-D ($P < .05$)
Delavar et al,[39] 2002	Double-blind	N = 20, age 16–26 y	*VAC* (preparation not specified; 30 drops) or placebo (30 drops); dosage twice/d at least 5 d before menstruation, 3 menstrual cycles	Placebo	COPE (retrospective)	VAS on 22 symptoms, responder rate (≥50% reduction in symptoms)	Significant decreases in VAS score in most symptoms after intervention; data of placebo not shown; responder rate significantly greater in intervention group compared to comparator group (70% vs 40%)
Di Pierro et al,[40] 2009[a]	First phase[c]: double-blind; second phase: open	N = 82, age >18 y	*VAC* (Monoselect Agnus, SIIT (Trezzano S/N, Milan, Italy) tablet 40 mg/d) or magnesium oxide (300 mg/d); after first phase of study *VAC* group was split into 2 groups with 21 patients as control without further treatment, and 21 patients receiving *VAC* 7 d before menstruation,[c] 3 menstrual cycles	Magnesium	DSM-III-R	VAS on 8 symptoms	First phase: significantly greater decrease on 7 of 8 symptoms in intervention group compared to control group ($P < .05$); second phase: improvement was significantly greater in intervention group compared to control group on 7 of 8 symptoms
He et al,[41] 2009[a]	Double-blind	N = 217, age 18–45 y	*VAC* (Agnucaston 40 mg/d) or placebo, 3 menstrual cycles	Placebo	PMTS score >18, 16 points increase in follicular phase compared to luteal phase, 2 mo prospective screening	PMSD, PMTS, responder rate (≥60% reduction in symptoms)	Significantly greater decrease on all outcome measures in intervention group compared to control group ($P < .05$)

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(continued)

TABLE 1
Characteristics of included studies in alphabetical order (N = 17) *(continued)*

Study	Study design	Patients	Intervention details	Comparator	Method of diagnosis	Outcome measures	Results
Kaplanoğlu and Aban,[42] 2015[a]	Single-blind,[c] 3 arms	N = 120, age 18–40 y	*VAC* (20 mg/d; preparation not specified) or EE-drs (30 μg ethinyl estradiol, 3 mg drospirenone; 21 tablets day 1–21) or placebo (10 drops of sterile water/d), 3 menstrual cycles	1) Placebo 2) Contraceptive	DSM-IV	VAS on 15 symptoms	Significant difference between groups on 10 of 15 symptoms ($P < .05$); significant decrease on most symptoms in all groups ($P < .05$)
Lauritzen et al,[43] 1997[a]	Double-blind	N = 127, age 18–45 y	*VAC* (Agnolyt [MADAUS GmbH, Köln, Germany]) 40 mg/d and 1 placebo daily), or pyridoxine (1 capsule of placebo twice daily on days 1–15 and 1 capsule of pyridoxine HCl [100 mg] twice daily on day 16–35), 3 menstrual cycles	Pyridoxine	PMTS (retrospective)	PMTS, responder rate (≥10-point improvement on PMTS score)	Significantly greater decrease in intervention group compared to control group on PMTS ($P = .04$); greater responder rate in intervention group compared to control group (26 vs 18 patients)
Mousavi et al,[44] 2015[a]	Double-blind	N = 72, mean age 20 y	*VAC* (40 drops/d; preparation not specified) or placebo (40 drops/d), 3 menstrual cycles	Placebo	DSM-IV	VAS (total scores on physical symptoms and psychological symptoms)	Significantly greater decrease in intervention group compared to control group on both outcome measures ($P < .05$)
Onaran et al,[45] 2003[a]	Blinding unknown	N = 124, age >18 y	*VAC* (Agnucaston 40 mg/d) or oral contraceptive (Miranova [Schering Germany, Istanbul, Turkey]); 100 μg /20 μg levonorgestrel/ethinyl estradiol/d), 3 menstrual cycles	Contraceptive	COPE, 2 mo prospective screening	COPE, HADS (depression), HADS (anxiety)	No significant difference between intervention and control groups on COPE and HADS (anxiety) ($P = .24$ vs $P = .48$); significantly greater decrease intervention group compared to control group on HADS (depression) ($P = .02$)
Pakgohar et al,[46] 2009[a]	Double-blind	N = 116, age >18 y	*VAC* (3.2–4.8 mg dry extract per tablet; 40 mg/d) or placebo, 2 menstrual cycles	Placebo	DSM-IV	DSR (total scores on physical symptoms and psychological symptoms)	Significantly greater decrease in intervention group compared to control group on DSR total scores ($P < .05$)

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TABLE 1
Characteristics of included studies in alphabetical order (N = 17) *(continued)*

Study	Study design	Patients	Intervention details	Comparator	Method of diagnosis	Outcome measures	Results
Risoleti et al,[47] 2011[a]	Blinding unknown, 3 arms	N = 72, age 17 −25 y	*VAC* (preparation not specified; 1 tablet/d) or 1 oral contraceptive pill/ d containing drospirenone (3 mg) and ethinylestradiol (30 μg) in 24/4 formulation or placebo, 3 menstrual cycles	1) Placebo 2) Contraceptive	DSM-IV	PMSD	Significantly greater decrease on PMSD total score in treatment groups compared to placebo group; no significant difference between 2 treatment groups
Salehi et al,[48] 2013[a]	Double-blind	N = 225, age 27.93 ± 8.94 y	*VAC* (preparation not specified, 1 tablet/d), or *Hypericum perforatum L* (preparation not specified, 3 tablets/d) or vitamin E 400 IU, 2 menstrual cycles	1) *Hypericum perforatum L* 2) Vitamin E	DSM-IV	PMSD	Significantly greater decrease in PMSD total score in intervention group compared to control groups ($P < .05$)
Scaldarella et al,[49] 2008	Double-blind	N = 60, mean age 30 y	*VAC* (Agnucaston; 41 mg/ d) or vitamin B6 (200 mg/ d), 3 menstrual cycles	Pyridoxine	PMTS (retrospective)	PMTS	Greater decrease in PMTS score in intervention group compared to control group (10 vs 6.6 points on PMTS)
Schellenberg,[50] 2001[a]	Double-blind	N = 178, age >18 y	*VAC* (ZE 440 [Max Zeller Söhne AG, Romanshorn, Switzerland]) extract 20 mg/d) or placebo, 3 menstrual cycles	Placebo	DSM-III-R	VAS (total score and on 6 symptoms), CGI-SI, responder rate (≥50% reduction in symptoms)	Significantly greater decrease on all outcome measures in intervention group compared to control group ($P < .05$), except for symptom "bloating"; greater responder rate in intervention group compared to control group (52% vs 24%)
Schellenberg et al,[51] 2012[a]	Double-blind	N = 162, age 18−45 y	*VAC* (ZE 440 extract 8 mg, 20 mg, or 30 mg/d) or placebo, 3 menstrual cycles	Placebo	DSM-III-R	VAS (total score and on 6 symptoms), responder rate (≥50% reduction in symptoms)	Significantly greater decrease on total symptom score and individual symptom scores in 20-mg group compared to control group and 8-mg group; significantly greater responder rate in intervention groups (20 mg, 30 mg compared to control group) ($P < .001$)

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TABLE 1
Characteristics of included studies in alphabetical order (N = 17) *(continued)*

Study	Study design	Patients	Intervention details	Comparator	Method of diagnosis	Outcome measures	Results
Turner and Mills,[52] 1993[a]	Double-blind	N = 600, age 18–46 y	*VAC* (1800 mg/d powdered dried berries) or placebo (soy-based placebo), 3 menstrual cycles	Placebo	Moos Menstrual Distress Questionnaire, retrospective	VAS on 5 symptoms	No significant difference between intervention and control group on 4 of 5 symptoms, except for "feel jittery or restless"
Zamani et al,[53] 2012[a]	Double-blind	N = 128, reproductive age	*VAC* (preparation not specified, 40 drops/d) or placebo (40 drops/d) in glass of fruit juice before breakfast from sixth day before menstruation until menstruation, 6 menstrual cycles	Placebo	DSM-IV	VAS on 6 symptoms	Significantly greater decrease in all symptoms in intervention group compared to control group ($P < .05$)

COPE, Calendar of Premenstrual Experiences; *DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSR*, Daily Symptom Report; *PMSD*, premenstrual syndrome diary; *PMTS*, Premenstrual Tension Self-Rating Scale; *VAC*, *Vitex agnus castus*; *VAS*, visual analog scale.

[a] Studies included in meta-analysis; [b] Written information from supplier of extract; [c] Written information from author.

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and volatile oils (monoterpenes, sesquiterpenes). The mechanism of action of *VAC* in the treatment of PMS has not been elucidated. In vitro studies show binding of *VAC* extracts to the dopamine-2 receptor,[18] the human opioid receptor,[19] and a selective binding affinity for the β-estrogen receptor.[20] The European Medicines Agency (EMA) has registered "well-established use" and "traditional use" of *VAC* for PMS.[21]

To our knowledge no systematic review or meta-analysis focusing explicitly on *VAC* in the treatment of PMS and/or PMDD has been published. Two systematic reviews focused on the treatment of PMS with herbal preparations including preparations of *VAC*[16,22] and a third looked into the use of *VAC* in female reproductive disorders.[23] While none of the 3 systematic reviews performed a complete meta-analysis, all 3 reviews are slightly positive about the effectiveness of *VAC* in the treatment of PMS and PMDD.

The objective of this systematic review and meta-analysis is to determine the efficacy, tolerability, and acceptability of *VAC* in the treatment of PMS and/or PMDD. We also explore clinical and design factors that influence efficacy results.

Objectives

To determine the efficacy, tolerability, and acceptability of *VAC* for the treatment of PMS symptoms, we will examine the following:

1. The effect of *VAC* on PMS symptoms vs placebo or comparator.
2. Harm outcomes (eg, discontinuation rates and adverse events).
3. The effect of *VAC* on patient satisfaction vs placebo or comparator.

Materials and Methods

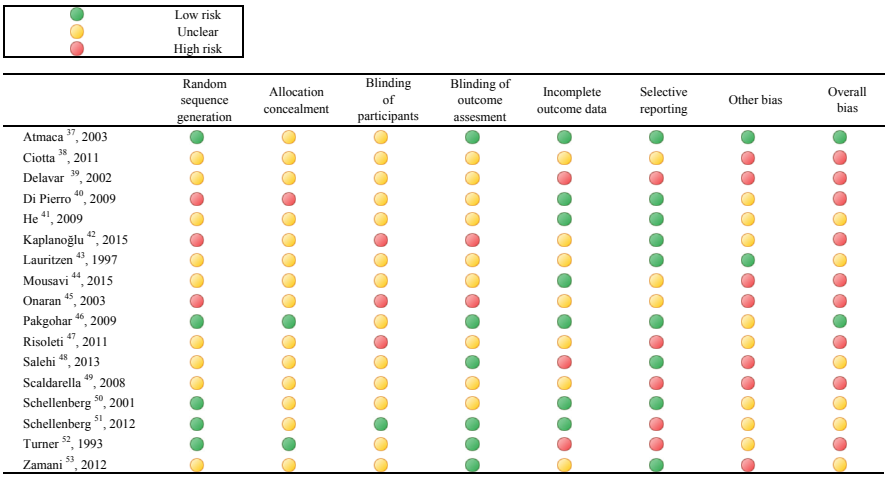
Protocol

The protocol of Shaw et al[24] was used as a guideline.

Eligibility criteria

We considered trials among women of reproductive age diagnosed with PMDD or PMS. Our review included studies using any diagnostic method, such as

FIGURE 2
Risk of bias of included studies



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Diagnostic and Statistical Manual of Mental Disorders (DSM) (III, III-R, IV, IV-TR, 5) and/or *International Statistical Classification of Diseases*,[25-27] Premenstrual Tension Self-Rating Scale (PMTS),[28] Moos,[29] Menstrual Distress Questionnaire (MDQ), or Calendar of Premenstrual Experiences (COPE).[30]

We included trials designed to reduce the symptoms of PMDD or PMS using any dose or preparation of *VAC*. Trials that studied homeopathic preparations of *VAC* and combinations of *VAC* with other treatments were excluded. The comparator could be placebo or pharmacotherapy (eg, antidepressant medication, phytotherapeutic agents, dietary supplements, or oral contraceptives).

We included all trials that evaluated the effect of *VAC* on PMDD or PMS symptoms at the end of the treatment period. Both physical and psychiatric symptoms were included.

We included all studies with a randomized controlled trial design and a minimal duration of 2 menstrual cycles. Conference abstracts, case series, and case reports were excluded. No language, publication date, or publication status restrictions were imposed.

Information sources and search strategy

In December 2014 a computerized literature search was designed and performed by the research team and an experienced biomedical information specialist. The following search terms were used: "premenstrual syndrome," "premenstrual tension," "premenstrual tension syndrome," "premenstrual dysphoric disorder," "late luteal," "late luteal phase dysphoric disorder," "late luteal phase disorder," "PMS," "PMT," "PMDD," "PMTS," "LLPD," or "LLPDD," and "*VAC*," "vitex," "agnus castus," "chaste tree," "chaste berry," "chaste-berry," "monk pepper," "hemp tree," "agnolyt," "cefanorm," "femicur," "gynocastus," "kytta-femin," "strotan," "agnomens," "agneau chaste," "gatillier," "keuschlamm," and "monnikspeper." A total of 10 databases were searched from inception onward: Embase (via embase.com), MEDLINE (via Ovid), Web-of-Science, Scopus, PsycINFO (via Ovid), Cinahl (via EBSCOhost), Cochrane Central (via Wiley), PubMed, Google Scholar, and AMED—Allied and Complementary Medicine Database (via Ovid). Additional articles were retrieved from PubMed by selecting only those articles that had not yet been indexed by MEDLINE. Gray literature was searched using Google Scholar. In addition to words in the title and abstracts for Embase, MEDLINE, PsycINFO, and Cinahl, we used thesaurus terms when available. Reference lists of key papers and review articles related to our subject were checked for records that might be missing. Manufacturers of *VAC* products described in a clinical study were approached to identify other published or unpublished trials and Clinical Trial Databases were searched (clinicaltrial.gov, International Clinical Trials Registry Platform search portal). The search was last updated on Jan. 13, 2016.

Study selection

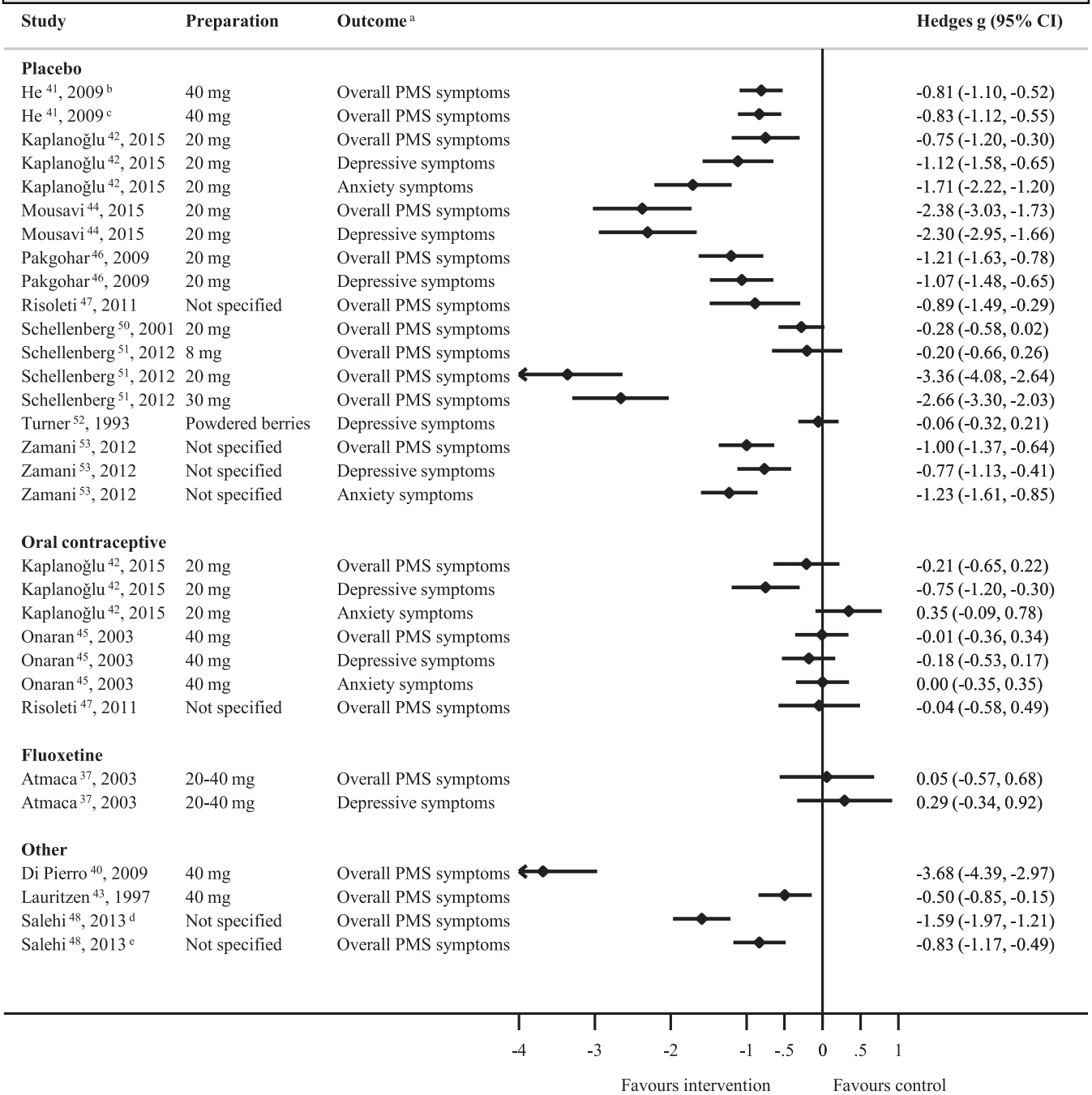
The EndNote X6 software package was used for record management.[31] After removing duplicates and records without abstracts, the remaining records were screened for eligibility on the basis of title and abstract. The eligibility of the full texts of the remaining records was assessed by 2 reviewers independently. If necessary, the manuscript was translated by a translator with a background in medicine. In cases in which multiple articles were based on the same trial, only the most complete data set was included. Disagreement between reviewers was resolved by the panel of all authors. The kappa statistic was used to calculate interrater agreement. A kappa value of 0.61-0.80 reflects substantial agreement and a kappa value of 0.81-1.00, (almost) perfect agreement.[32]

Data extraction

Data collection was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[33,34] Using a data extraction form, 2 reviewers extracted data independently. Differences in extracted data were discussed by all the authors. Due to inconclusive information on the design and outcome measure, we contacted the authors of all included papers. Additionally, 2 authors were contacted to check whether multiple papers had been published on a single trial.

The following data items were extracted from the included papers: characteristics of the study design, characteristics of the patient population and sample size directly after randomization, intervention details, type of comparator, method of diagnosis, outcome measures, and overall results. As outcome measures, we extracted data

FIGURE 3
Forest plot of included studies stratified by comparator



Treatment effects of *Vitex agnus castus* (N=14; 31 effect sizes) are expressed in Hedges g and 95% confidence intervals (CI). The solid vertical line corresponds to no effect of treatment. [a]Overall premenstrual syndrome (PMS) symptoms are assessed using the following instruments: PMS diary, Premenstrual Tension Self-Rating Scale, Daily Symptom Report, Calendar of Premenstrual Experiences, and PMS visual analog scale; Depressive symptoms are assessed using Beck Depression Inventory, Hamilton Depression Rating Scale, Mood Disorders Questionnaire, or visual analog scale; Anxiety symptoms are assessed using anxiety subscale of the Hamilton Depression Rating Scale, or visual analog scale. [b]Assessed using PMS diary. [c]Premenstrual Tension Self-Rating Scale. [d]*Hypericum Perforatum* used as control. [e]Vitamin E used as control.

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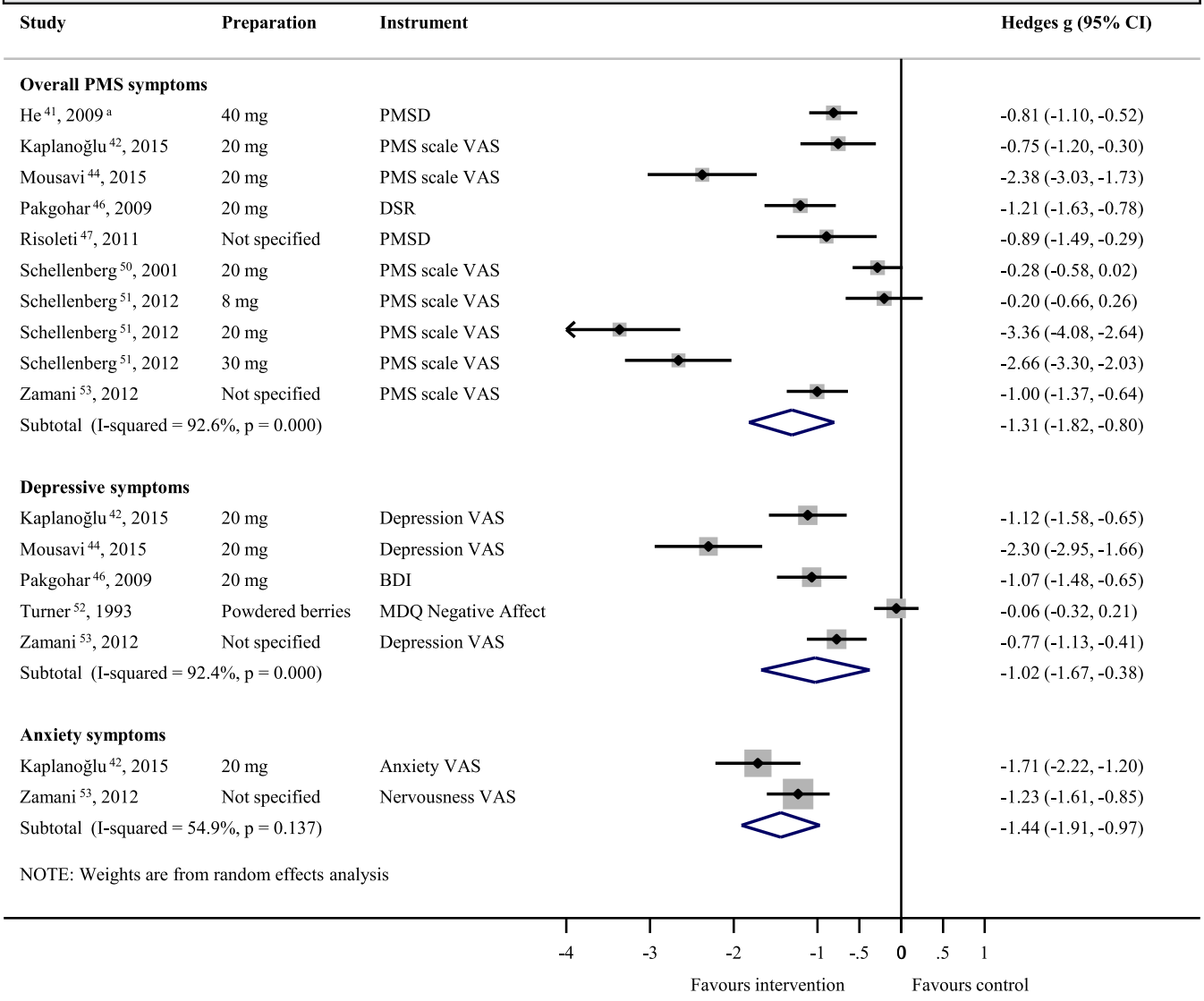
FIGURE 4
Forest plot of placebo-controlled studies stratified by outcome



Treatment effect of *Vitex agnus castus* (N=9; 17 effect sizes) are expressed in Hedges g and 95% confidence intervals (CI). The blue diamond reflects the weighted treatment effect. Area of gray square reflects the weight each comparison contributes to the meta-analysis. Abbreviations of the instruments used: PMSD (PMS diary); PMS scale VAS (PMS visual analog scale); DSR (Daily Symptom Report); Depression VAS (visual analog scale); BDI (Beck Depression Inventory); MDQ (Mood Disorders Questionnaire); Anxiety VAS (visual analog scale); Nervousness VAS (visual analog scale). [a]To avoid the inclusion of multiple outcomes in the analysis the results of the study by He[41] assessed using the Premenstrual Tension Self-Rating Scale were excluded from this subset.

BDI, Beck Depression Inventory; *DSR*, Daily Symptom Report; *MDQ*, Moos Menstrual Distress Questionnaire; *PMS*, premenstrual syndrome; *PMSD*, premenstrual syndrome diary; *VAS*, visual analog scale.

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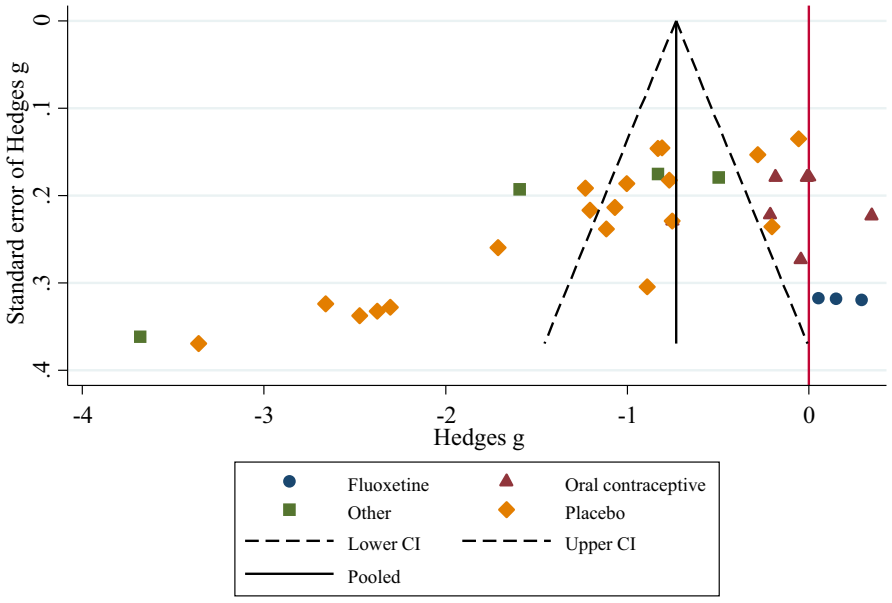
on the presence and/or severity of physical and psychiatric symptoms of PMS and/or PMDD at baseline and follow-up and accompanying test statistics. Because many trials used multiple outcome measures, we preferred outcomes assessed with validated instruments, ie, PMS Diary, PMTS, Daily Symptom Report, COPE, Daily Record of Severity of Problems, and visual analog scales to assess overall PMS symptoms, and Beck Depression Inventory, Hamilton Depression Rating, Mood Disorders Questionnaire, and psychiatric subscales of PMS questionnaires and visual analog scales to assess specific depressive and anxiety PMS symptoms for inclusion in our meta-analysis. If item scores were reported separately, we calculated scale sum scores. Additionally, we assessed harm outcomes (eg, discontinuation rates and adverse events) and patient satisfaction as reported by the authors.

The reviewers independently rated the risk of bias for each trial according to the Cochrane Risk of Bias Tool.[25] Publication bias was assessed visually with a funnel plot, and with Egger test we assessed formally whether the effect size decreased in proportion to increasing sample size.[26] Plots with a symmetrical funnel shape indicate little or no publication bias. However, since smaller or nonsignificant trials are less likely to be published, trials in the bottom left-hand corner of the plot are often missing.

Synthesis of results

Analyses were stratified for overall PMS symptoms and specific psychiatric PMS symptoms within the subset of placebo-controlled studies. In each stratum, we calculated pooled estimates using bias-corrected standardized mean estimates, ie, Hedges g, with 95% CI between the intervention group and the control group at the end of the trial. Hedges g corrects for differences in variances resulting from the inclusion of trials with varying sample sizes. The magnitude of Hedges g can be interpreted as small (0.20), moderate (0.50), or large (0.80). As was the case in the majority of included trials, we used the results according to per protocol analysis. The results were represented in a forest plot. Random effects analysis was used to estimate a pooled treatment effect since it produces a more reliable estimate than fixed effect analysis when there is substantial heterogeneity. Cochran Q test, I-squared (I^2), and T-squared (T^2) statistics were used to quantify heterogeneity across trials. Heterogeneity was further explored by conducting sensitivity analyses within the subset of placebo-controlled trials with overall PMS symptoms as outcome. For this purpose we calculated the pooled treatment effect using both fixed and random effects modeling and informally evaluated the impact of the modeling procedure on the pooled treatment effect.[25] We also created subgroups of trials based on: (1) *VAC* dosage (≤20 vs 20-40 mg), (2) custom-made vs commercially available *VAC* extracts, and (3) overall trial quality (ie, high vs moderate risk of bias), and specific study elements based on (4) allocation concealment (insecure vs unknown) and (5) blinding of trial participants (securely blinded vs insecurely blinded vs unknown), (6) reporting biases (present vs absent), and (7) symptom assessment (using validated symptom scales vs single items). Fixed effect estimation was used to compare differences across categories. Standardized effect sizes were calculated using comprehensive meta-analysis.[27] Further statistical analyses were performed using the "metan package" in Stata 13.[35,36]

FIGURE 5
Funnel plot of included studies stratified by comparator



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Results

Selection of studies

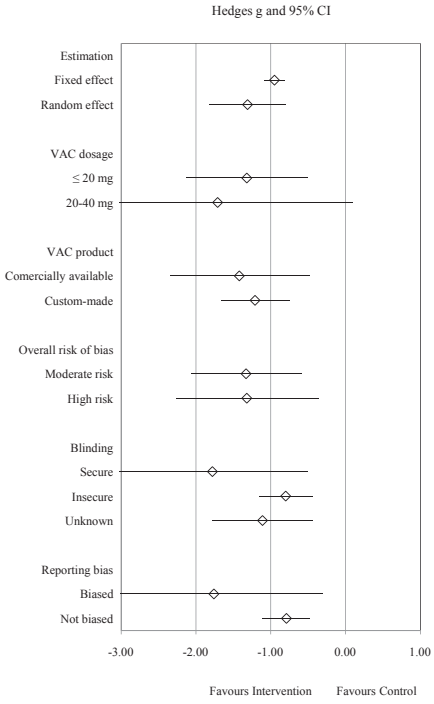
Figure 1 shows the PRISMA 2009 flow diagram of the included and excluded studies. The titles and abstracts of 395 papers were screened, after which 357 of these papers were excluded. In all, 38 full-text articles were assessed for eligibility. Articles based on parts of 2 trials were published in 5 different publications; for these 2 trials the most complete data sets were included in our meta-analysis and duplications were excluded. Ultimately we were able to include 17 randomized controlled trials of *VAC* in the treatment of PMS in our qualitative analysis.[37-53] Fourteen of these could be included in the quantitative analysis.[37,40-48,50-53] Other studies were excluded because insufficient quantitative data were reported. The interrater reliability was considered good (raw interrater agreement, 87.5%; kappa, 0.69; 95% CI, 0.41−0.97).

Study characteristics

Study characteristics are summarized in Table 1. Eight articles were written in English,[37,40,41,43,50-53] 4 in Farsi,[39,44,46,48] 3 in Italian,[38,47,49] and 2 in Turkish.[42,45]

All included articles describe randomized controlled trials, but the method of randomization was unclear in 9 studies.[38,39,41,43,44,46,48,49,53] Thirteen trials were double-blinded, according to the papers. In the studies by Onaran et al[45] and Risoleti et al,[47] blinding of participants and/or raters was not described. The studies by Atmaca et al[37] and by Kaplanoğlu and Aban[42] were single-blind. Ten trials were placebo-controlled,[39,41,42,44,46,47,50-53] while 9 trials were comparator-controlled (fluoxetine,[37,38] an oral contraceptive,[42,45,47] pyridoxine,[43,49] magnesium[40]) and in 1 study *Hypericum*

FIGURE 6
Vitex agnus castus treatment effect for different subgroups of studies



Treatment effect of *Vitex agnus castus* (*VAC*) of placebo-controlled studies with overall PMS symptoms as outcome (N=8; 10 effect sizes) using fixed and random effect estimation, and for different subgroups of studies (N=9). Pooled effect sizes for subgroups of studies are estimated using random effects estimation.

CI, confidence interval.

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perforatum L and vitamin E[48] were used as comparators. Two of the trials compared *VAC* with an oral contraceptive and a placebo.[42,47]

The studies diagnosing PMS with stringent criteria included patients with PMDD according to the DSM-III or DSM-IV criteria (11 trials)[37,38,40,42,44,46-48,50,51,53] or with a diagnosis after prospective self-rating on either the COPE[45] or the PMS Diary.[41,43] The other studies (N = 3) were included in the group PMS with broad criteria, since PMS was diagnosed retrospectively by Moos[29] Menstrual Distress Questionnaire,[52] PMTS,[49] or the COPE.[39]

Seven different *VAC* preparations were specified in 11 of the 17 trials (Table 1). Six of these preparations were extracts and 1 consisted of capsules of the dried powdered berries. The other 6 trials did not specify the preparation.[39,42,44,47,48,53] In 8 studies commercially available extracts were used: Agnucaston (Schering Germany, lstanbul, Turkey),[37,41,45,49] Monoselect Agnus (SIIT Trezzano S/N, Milan, Italy),[40] Agnolyt (MADAUS GmbH, Köln, Germany),[43] and ZE 440 (Max Zeller Söhne AG, Romanshorn, Switzerland).[50,51] In 7 trials, 40 mg of extract was administered every day throughout the entire cycle. Five trials used lower dosages (ranging from 8-30 mg) daily. One trial administered the preparation (unspecified) only from the sixth day before menstruation until menstruation.[53]

Nine different primary outcome measures were employed (Table 1). Two trials evaluated not only total symptom scores but also individual symptom scores.[50,51] Several dichotomous variables were used as secondary outcome parameters, including patients who no longer had any symptoms,[43] 50% reduction in symptoms,[39,50,51] 60% reduction in symptoms,[41] "PMS generally improved," and "worsening of PMS symptoms" according to patients.[52] In the study by Schellenberg[50] the tolerability of the treatment was assessed on a 5-point scale by researchers and patients at the end of the treatment.

Efficacy

Ten of the 17 studies compared a *VAC* preparation to placebo. All but 1 study reported positive results, despite the use of different outcome scales, *VAC* preparation, dosage (extracts ranging from 8-41 mg), and dosing regimens (once daily throughout the entire menstrual cycle or 6 days before menstruation[53]). The only negative study used ground berries as preparation[52] whereas all the other studies used an extract. Three studies compared *VAC* with an oral contraceptive and found that the efficacy of *VAC* was comparable to that of oral contraceptives.[42,45,47] Two of these studies had a third placebo condition that appeared to be inferior to *VAC* and the oral contraceptive on total PMS scores.[42,47] Fluoxetine was used as comparator in 2 studies.[37,38] One of these found superior efficacy on 4 items of the Hamilton depression rating scale in the control group, while the other found no difference. Superior efficacy of *VAC* was found in trials with pyridoxine,[43,49] magnesium,[40] *Hypericum perforatum L*, and vitamin E as comparators.[48]

Risk of bias of included studies

The results of the risk of bias assessment are shown in Figure 2. There are only 2 studies for which the reviewers rate the risk of bias within the studies as low. Six studies have a moderate risk of bias, while 9 studies are rated as having a high risk of bias. Reporting was incomplete for all trials included. In particular, essential information was missing regarding the procedures followed to ensure allocation concealment (14 studies) and blinding of the participants (13 studies).

Efficacy: quantitative synthesis of results

The quantitative selection included 14 trials. Seven articles[37,41,42,44-46,53] provided multiple outcomes, while 3 reported on ≥3 treatment arms.[42,47,48] Kaplanoğlu and Aban[42] used both multiple treatment arms and multiple treatment outcomes. In total, 31 effect sizes were estimated using data from 1786 individual patients. In Figure 3 the standardized effects of *VAC* in all included trials are plotted and stratified by comparator, irrespective of dosage and outcome. The pooled effect of *VAC* in placebo-controlled trials was large (Hedges g, −1.21; 95% CI, −1.53 to −0.88; I^2, 91%). Compared to oral contraceptives and fluoxetine the pooled treatment effect of *VAC* was small (Hedges g, −0.12; 95% CI, −0.35 to 0.11; I^2, 54%; and Hedges g, 0.17; 95% CI, −0.27 to 0.61; I^2, 0%, respectively). Against vitamins, supplements or other herbal comparators the effect of *VAC* was large (Hedges g, −1.60; 95% CI, −2.60 to −0.61; I^2, 96%). Since there is a very high degree of heterogeneity and multiple effect sizes from single studies were included, these pooled

TABLE 2
All-cause discontinuation and discontinuation due to adverse events of all included studies in alphabetical order (N = 17)

Study	No. of patients in intervention group	No. of patients in control group	All-cause discontinuation intervention group	All-cause discontinuation control group	Due to adverse events in intervention group	Due to adverse events in control group	Reported adverse events in intervention group	Reported adverse events in control group
Atmaca et al,[37] 2003	19	19	5%	10%	5%	10%	Nausea (N = 5), headache (N = 4)[a]	Nausea (N = 6), headache (N = 4), insomnia (N = 3), sexual dysfunction (N = 2)[a]
Ciotta et al,[38] 2011	31	26	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Delavar et al,[39] 2002	10	10	33%	33%	Not reported	Not reported	Nausea and vomiting (N = 3), hypermenorrhea (N = 1)[b]	
Di Pierro et al,[40] 2009	42	40	0%	0%	0%	0%	Acne (N = 1), urticaria (N = 1)	Acne (N = 2), urticaria (N = 1)
He et al,[41] 2009	104	104	6%	7%	2%	2%	Headache (N = 2)[a]	Headache (N = 2)[a]
Kaplanoğlu and Aban,[42] 2015	40	40 (Oral contraceptive) 40 (Placebo)	0%	0%	0%	0%	Not reported	Not reported
Lauritzen et al,[43] 1997	61	66	46%	34%	1%	2%	Skin reactions (N = 2), headache (N = 1), unspecified adverse events (N = 9)	Unspecified adverse events (N = 5)
Mousavi et al,[44] 2015	36	36	17%	14%	8%	11%	Pruritus (N = 2), gastrointestinal disturbances (N = 1)	Unspecified adverse events (N = 4)
Onaran et al,[45] 2003	61	63	Not reported	Not reported	Not reported	Not reported	None	Headache (N = 2), nausea (N = 1), weight gain (N = 7)
Pakgohar et al,[46] 2009	49	50	16%	14%	5%	3%	Headache (N = 7), bloating (N = 7)[a]	Headache (N = 7), bloating (N = 8)[a]

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(continued)

TABLE 2
All-cause discontinuation and discontinuation due to adverse events of all included studies in alphabetical order (N = 17) *(continued)*

Study	No. of patients in intervention group	No. of patients in control group	All-cause discontinuation intervention group	All-cause discontinuation control group	Due to adverse events in intervention group	Due to adverse events in control group	Reported adverse events in intervention group	Reported adverse events in control group
Risoleti et al,[47] 2011	27	25 (Oral contraceptive) 20 (Placebo)	Not reported	Not reported	Not reported	Not reported	2 Adverse events (urticaria, headache)	Placebo: 2 adverse events (acne, gastric disturbances, early menstrual period) Contraceptive: 4 adverse events (spotting, acne, depression, water retention)
Salehi et al,[48] 2013	70	70 (*Hypericum perforatum L*) 70 (Vitamin E)	0%	0%	0%	0%	Not reported	Not reported
Scaldarella et al,[49] 2008	30	30	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Schellenberg,[50] 2001	86	84	7%	4%	0%	0%	Acne (N = 1), multiple abscesses (N = 1), intermenstrual bleeding (N = 1), urticaria (N = 1)	Acne (N = 1), early menstrual period (N = 1), gastrointestinal disturbances (N = 1)
Schellenberg et al,[51] 2012	36 (8 mg) 35 (20 mg) 36 (30 mg)	35	15%	17%	0%	0%	8 mg: Mild headache (N = 1), mild interim spotting (N = 1); 20 mg: mild hypertension (N = 1); 30 mg: headache (N = 1), vaginal fungal infection (N = 1), abdominal bloating (N = 1), impure skin (N = 1)	No toleration of drug in morning (N = 1), malaise after intake (N = 1), severe headache (N = 1)
Turner and Mills,[52] 1993	105	112	65%	63%	Not reported	Not reported	Not reported	Not reported
Zamani et al,[53] 2012	62	66	0%	0%	0%	0%	None	None

[a] Only most frequently experienced adverse events were reported; [b] Unclear in which group these adverse events were reported.

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treatment effects should be viewed as merely exploratory.

The standardized treatment effects of *VAC* within the subset of placebo-controlled trials (9 studies, 17 effect sizes) are plotted in Figure 4. With regard to overall PMS symptoms, a large pooled treatment effect was found of −1.31 (Hedges g; 95% CI, −1.82 to −0.80; I^2, 93%). As regards depressive symptoms associated with PMS, Hedges g was −1.02 (95% CI, −1.67 to −0.38; I^2, 92%) and for anxiety symptoms Hedges g was −1.44 (95% CI, −1.91 to −0.97; I^2, 55%). Again, heterogeneity is very high, so that pooled treatment effects should be interpreted with extreme caution.

Publication bias

Figure 5 shows a funnel plot stratified by comparator. This plot turns out to be very asymmetrical. A large proportion of trials are placed outside the 95% confidence limits (20/31 effect sizes), and we see an increase of the effect size with decreasing sample sizes. Egger tests suggest the presence of bias in both the full set of studies (14 studies; 31 effect sizes) (intercept, −5.71; 95% CI, −10.09 to −1.34; $P = .012$) and in the subset of placebo-controlled studies with overall PMS symptoms as outcome (8 studies; 10 effect sizes) (intercept, −8.65; 95% CI, −14.93 to −2.37; $P = .013$).

Heterogeneity and sensitivity analyses

The results of the sensitivity analyses to test bias and potential sources of heterogeneity within the subset of placebo-controlled studies using overall PMS symptoms as outcome measure are depicted in Figure 6. Fixed and random estimation procedures resulted in different pooled effects, ie, fixed: Hedges g, −0.95; 95% CI, −1.09 to −0.82; and random: Hedges g, −1.31; 95% CI, −1.82 to −0.80.

VAC dosage made no difference to the treatment effect (degrees of freedom [df], 1; Cochran Q test, 2.46; $P = .117$; $I^2_{\leq 20\ mg}$, 96%; $I^2_{20\text{-}40\ mg}$, 95%). However, commercially available *VAC* products showed a larger effect size (Hedges g, −1.42; 95% CI, −0.48 to −2.35; I^2, 96%) than custom-made products (Hedges g, −1.21; 95% CI, −0.75 to −1.66; I^2, 78%) (df, 1; Q, 4.39; $P = .036$). With regard to the overall risk of bias of the study, we found no significant impact on treatment effect (df, 1; Q, 2.88; $P = .089$; $I^2_{high\ risk}$, 86%; $I^2_{moderate\ risk}$, 95%). We found a significant impact of blinding on effect size (df, 2; Q, 10.56; $P < .05$). Larger effects were found in securely blinded studies (Hedges g, −1.78; 95% CI, −0.50 to −3.06; I^2, 96%) than in insecurely blinded studies (Hedges g, −0.80; 95% CI, −0.44 to −1.16; I^2, 0%) and in studies that did not report on blinding (Hedges g, −1.11; 95% CI, −0.63 to −1.79; I^2, 92%). I^2 values within subgroups remained large. The impact of allocation concealment could not be assessed, since only 1 of the included studies[43] provided enough information to ascertain bias. We also found a larger effect size in studies suspected of selective reporting (Hedges g, −1.76; 95% CI, −0.31 to −3.21; I^2, 96%) than in studies without reporting bias (Hedges g, −0.79; 95% CI, −0.48 to −1.11; I^2, 75%). Again, I^2 values within subgroups of studies were large (df, 1; Q, 14.31; $P < .05$). Since none of the placebo-controlled studies had assessed overall PMS symptoms using a single item, we were unable to calculate the impact of the outcome assessment used.

Discontinuation rates, adverse events, and patient satisfaction

Thirteen of the trials reported all-cause discontinuation (Table 2). The dropout rates ranged from 0-46% and were evenly distributed among participants in the *VAC* and comparator groups. Eleven of the trials reported adverse events (Table 2). Of 492 patients, 59 (12.0%) treated with *VAC* reported an adverse event compared to 29 of 328 patients (8.8%) treated with placebo. All adverse events observed with the treatment of *VAC* were mild and did not differ from those occurring with the placebo treatment. No serious adverse events were reported in any trial with *VAC*. The study comparing *VAC* with fluoxetine (no placebo arm) reported a higher number of adverse events in general and specifically nausea and headache in the fluoxetine group.[37] Onaran and coworkers[45] reported 10 patients in the Miranova group with side effects that occur commonly during treatment with contraceptives, such as headache, nausea, and weight gain. There were no side effects in the *VAC* group. In the study by Schellenberg and co-workers[51] tolerability was assessed by researchers and patients separately at the end of the treatment on a 5-point scale. Both ratings indicated the tolerability of 20 mg of ZE 440 as very good (69% and 91%, respectively) to good (31% and 9%, respectively). Two thirds of the patients in the 20-mg and 30-mg ZE 440 group wished to continue with the medication taken during the trial as opposed to 38% of the 8-mg ZE 440 group. None of the other articles reported on patient satisfaction.

Comment

Main findings

The included studies were executed on 2 continents and in 6 countries. The trials used a variety of diagnostic and severity criteria and many different *VAC* preparations, outcome measures, and endpoints were involved. Thirteen of 14 studies with placebo, dietary supplements, or herbal preparations as controls reported positive effects of *VAC* on total PMS symptoms, with adverse events not different from those occurring with the placebo or comparator. We found large effect sizes for efficacy (Hedges $g_{placebo}$, −1.21; 95% CI, −1.53 to −0.88 and Hedges $g_{supplements\ and\ herbs}$, −1.60; 95% CI, −2.60 to −0.61). Meta-analysis focusing on the depressive symptoms (5 studies) and anxiety symptoms (2 studies) of PMS also shows large effect sizes. The comparison of oral contraceptives or fluoxetine with *VAC* reveals no statistical difference regarding efficacy (Hedges $g_{oral\ contraceptives}$, −0.12; 95% CI, −0.35 to 0.11, and Hedges $g_{fluoxetine}$, 0.17; 95% CI, −0.27 to 0.61). However, fewer adverse events occurred with *VAC* than with oral contraceptives or fluoxetine. These results show that *VAC* extracts are not superior in efficacy compared to SSRIs or oral contraceptives, but are potentially effective compared to placebo, dietary supplements, and other herbal preparations.

Strengths and limitations

The current paper is a systematic review of treatment with *VAC* in PMS/PMDD based on a thorough systematic search without language limitation, a thorough evaluation of trial quality, followed by an extensive meta-analysis. We also analyzed the psychiatric symptoms of PMS. In addition we explored the impact of clinical and design factors to find an explanation of the high degree of heterogeneity.

We found several factors that preclude a definite conclusion on the efficacy of *VAC* for PMS or PMDD. Firstly, the efficacy outcomes of these studies show extremely high statistical heterogeneity (>90%) so that combining the results into an overall effect of *VAC* might be considered misleading.[54] We were unable to single out distinct factors that might satisfactorily explain this heterogeneity. It seems an explanation must be sought in a combination of several substantial clinical and methodological differences and/or the impact of additional unidentified differences among the studies.

In addition, the overall quality of the included studies was low. Only 2 studies were considered of moderate quality, and none was considered of high quality. Reporting was found to be incomplete for all included studies, especially with respect to allocation concealment and blinding procedures. This finding seems to be characteristic of publications about randomized controlled trials of the effect of complementary alternative medicine interventions.[55,56] Larger effect sizes were reported in studies that were suspected of selective reporting than in studies without reporting bias. These findings were in line with previous systematic reviews, which found that more rigorous studies of both conventional and complementary alternative medicine yield less positive treatment effects.[57-59]

Apart from methodological biases in the included trials, we found strong evidence of publication bias, in other words, smaller studies reporting larger effects were more often represented among the publications included, and a large proportion of the publications included were located outside the 95% CI of our funnel plot. Many trials of *VAC* were published in low-impact-factor journals.[60] As a result, we conclude that, at best, the reported *VAC* treatment effects overestimate the real treatment effect of *VAC* on PMS symptoms.

Comparison with existing literature

This review included 17 trials, whereas the systematic reviews of Whelan et al,[16] Dante and Facchinetti,[22] and Van Die et al[23] included 4, 4, and 10 trials, respectively. The study of Ma et al[61,62] describes a subpopulation of the larger multicenter trial of He and co-workers.[41] Therefore, we excluded the study of Ma and co-workers[61,62] from our analysis, while both the reviews of Dante and Facchinetti[22] and Van Die and colleagues[23] erroneously included this trial in their reviews. All 3 reviews employed different protocols, a language restriction was imposed by Whelan and coworkers,[16] the types of interventions were not specified in any of the reviews, and types of outcome measures were not specified in Whelan and coworkers[16] or Dante and Facchinetti.[22] Dante and Facchinetti[22] and Whelan and coworkers[16] did not use the Cochrane Risk of Bias tool to assess the quality of the included trials. Because of the heterogeneity of the included studies, the first 2 reviews refrained from conducting a meta-analysis, while Van Die et al[23] only performed a meta-analysis on 2 of the 10 included studies. Despite these limitations, all 3 reviews are slightly positive about the effectiveness of *VAC* in the treatment of PMS and PMDD. Terms used to describe its effectiveness are "possibly effective,"[16] "seem useful,"[22] and "suggest benefit."[23]

Conclusions and implications

There is a definite need for high-quality trials of appropriate size and duration (at least 3 months) to examine the effect of standardized commercially available extracts of *VAC* (20-40 mg/d) in comparison to placebo. PMDD should be diagnosed according to the criteria of DSM-5.[4] The Daily Record of Severity of Problems could be used for prospective daily ratings during at least 2 consecutive symptomatic cycles to diagnose both PMDD and PMS. It is also recommended that this validated scale is used as an outcome measure.[63] For adequate reporting of trials the Consolidated Standards of Reporting Trials guidelines should be followed.[64] If *VAC* appears superior over placebo in a well-designed study, we recommend as next step a noninferiority trial with extracts of *VAC* in comparison with SSRIs and/or oral contraceptives. Future systematic reviews should be restricted to high-quality trials.

Although the EMA accepts *VAC* in its "well-established use" and "traditional use" categories for PMS and the relevant guideline of the Association of Reproductive Health Professionals includes *VAC* as a treatment option, we must conclude that so far there is no convincing and conclusive evidence that *VAC* effectively reduces symptoms of PMS or PMDD. However, clinicians are often confronted with varying degrees of uncertainty and may therefore offer women with PMS or PMDD a trial with *VAC* if they have contraindications, intolerance, or a personal aversion to SSRIs and oral contraceptives, since *VAC* is likely to be a safe treatment,[21] should result at least in a placebo effect,[11] and may perhaps be of real pharmacological benefit. ■

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