

## Use of *Vitex agnus-castus* in migrainous women with premenstrual syndrome: an open-label clinical observation

Anna Ambrosini · Cherubino Di Lorenzo ·  
Gianluca Coppola · Francesco Pierelli

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**Abstract** Premenstrual syndrome (PMS) affects most women during their reproductive life. Headache is regarded as a typical symptom of PMS and, close to menses, migrainous women could experience their worst migraine attacks. *Vitex agnus-castus* (VAC) is a phytopharmaceutical compound, considered worldwide to be a valid tool to treat PMS. Aim of this study is to explore if headache is ameliorate in migrainous women treated with VAC for PMS by an open-label clinical observation. Migrainous women with PMS were enrolled in the study and advised to assume a treatment with VAC (40 mg/day) for PMS for a 3-month period. Effects both on PMS and headache were assessed. Out of 107 women, 100 completed the 3-month treatment for PMS. Out of them, 66 women reported a dramatic reduction of PMS symptoms, 26 a mild reduction, and 8 no effect. Concerning migraine, 42 % of patients experienced a reduction higher than 50 % in frequency of monthly attacks, and 57 % of patients experienced a

reduction higher than 50 % in monthly days with headache. No patients reported remarkable side effects. Pending a placebo-controlled trial to confirm our results, we observed that the use of VAC in migrainous women affected by PMS resulted to be safe and well tolerated, and may positively influence the frequency and duration of migraine attacks.

**Keywords** *Vitex agnus-castus* · Premenstrual syndrome · Migraine · Chaste Tree · Chasteberry

### Introduction

Most women (70–90 %) experience premenstrual symptoms [1]. A collection of these symptoms, that occurs regularly during the 2 weeks prior to menses and vanishes after the menstrual flow starts (and sufficiently severe to interfere with some aspects of life), is named premenstrual syndrome (PMS). Most common PMS symptoms are breast swelling and tenderness, acne, bloating and weight gain, pain (headache or joint pain), food cravings, and psychological and emotional features (irritability, mood swings, crying spells, depression) [2]. Prevalence of PMS is estimated around 20–40 % of childbearing-age women [1], and this fluctuation is due to not well codified diagnostic criteria for PMS. In fact, PMS prevalence could vary widely in the same population across different adopted diagnostic criteria [3]. A more severe form of PMS, regarded as a specific psychiatric disorder, and characterised by a well-designated sequence of symptoms (at least 5), is named premenstrual dysphoric disorder (PMDD) [4]. PMDD is rarer than PMS (3–8 %) [1], and accounts for a high impairment in a woman's quality of life and a social cost, in terms of loss of work hours, drug purchases, medical visits, and Emergency Department admissions [5].

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A. Ambrosini and C. Di Lorenzo contributed equally to this study.

A. Ambrosini (✉) · F. Pierelli  
INM Neuromed, IRCCS, Headache Clinic,  
via Atinense, 18, 86077 Pozzilli (Isernia), Italy  
e-mail: anna.ambrosini@neuromed.it

C. Di Lorenzo  
Don Carlo Gnocchi Onlus Foundation, Rome, Italy

G. Coppola  
Department of Neurophysiology of Vision and  
Neurophthalmology, G.B. Bietti Eye Foundation-IRCCS,  
Rome, Italy

F. Pierelli  
Department of Medical and Surgical Sciences and  
Biotechnologies and ICOT, "Sapienza" University of Rome,  
Polo Pontino, Latina, Italy

Headache, with undefined clinical characteristics, is regarded as a symptom of PMS. In fact, in migrainous women there is a close relationship between female sex hormone fluctuation and migraine [6], as ratified in the second edition of the International Classification of Headache Disorders (IHDR-II) by the proposal of diagnostic criteria for menstrual-related migraine (A1.1.1 and A1.1.2), even if a wide consensus on this form of headache is still lacking [7]. However, a woman affected only by a pure menstrual-related migraine is rare; the majority of patients are migraineurs who experience the worst headache attack (more severe, longer, refractory to treatment) in correspondence of menses, or during the premenstrual period, with respect to the headache attacks occurring outside the perimenstrual period [8]. So that it seems much likely that in migrainous women the headache featuring in PMS is a true migraine attack.

Different therapeutic strategies have been proposed for PMS treatment, ranging from lifestyle modification to induction of early menopause by surgical procedures (oophorectomy) [8], but the pharmacological approach results to be widely used, and among different drugs, phytopharmaceutical products find a broad application [8–11]. In particular, *Vitex agnus-castus* (VAC) was reported to be effective on PMS [12–15], cyclical mastalgia and hyperprolactinemia [16–18], and showed a good safety profile [19].

Accidental reports from several patients of ours suggested a benefit on their headache (both menstrual than non-menstrual related) in consequence of assumption of VAC, prescribed by general practitioner or gynaecologist to treat PMS: that observation induced us to investigate in a prospective open-label study this compound in migrainous women with PMS, to better assess its effects on their migraine attacks.

## Patients and methods

### Study design

This is an open-label observational study on the use of VAC in migrainous women suffering from PMS.

Protocol of the study and the ‘patient informed consent form’ were approved by our local Ethic Committee.

Every patient was advised to assume a preparation of VAC 40 mg/die for a quarterly period. To be sure that the same dose of VAC was to be assumed by all patients (being herbal drugs, dosages sometimes are not standardised), the same industrially made, and worldwide marketed, preparation of VAC (Cyclodynon<sup>TM</sup> 40 mg, produced in Germany by Bionorica AG. and distributed in Italy as food integrator by Theramex) [20] was prescribed.

### Patients

Patients were enrolled in the tertiary care Headache Clinic of INM Neuromed (Pozzilli, Isernia, Italy), among outpatients affected by episodic migraine without aura (IHDR-II code 1.1) who were already being followed from more than 3 months (new patients were excluded). Patients were informed that they will receive a 3-months ‘in-label’ treatment for their PMS, to assess its effectiveness also on migraine, and a written consent was obtained.

Inclusion criteria were presence of a severe form of PMS, constant for more than 1 year; no headache prophylaxis in the last 3 months, or, whether in prophylactic treatment, no modifications of therapy dosages during the previous 4 months. Exclusion criteria were pregnancy or breastfeeding, use of hormonal contraceptives, a severe physical or mental illness, presence of a second type of headache, or presence of medication overuse.

### Clinical assessment

Presence of PMS was assessed by anamnesis [1]. This study was not aimed to investigate how VAC is useful in PMS, as it was already suggested [21], but whether it can be of any utility on the headache of migrainous women suffering from PMS, while treating their PMS. That is why PMS diagnosis and staging was not formulated and followed by questionnaires used for clinical trials but, as usual in a typical clinical setting, simply verifying the presence of at least one group of the following symptoms in the premenstrual period: pain symptom, apart from headache; bloating, weight gain and/or liquid retention; psychological and emotional features (irritability, mood swings, crying spells, depression) [1, 2, 21]. These symptoms had to invalidate patients, limiting their activities and requesting the use of medical treatments (analgesics, diuretics, benzodiazepines, antidepressants, etc.). Also diagnosis of migraine without aura was performed by anamnesis, according to the diagnostic criteria provided by the International Classification of Headache Disorders-IInd Edition (IHDR-II) [7]. All patients recorded their headache data (frequency and duration of attacks) on a daily headache diary that includes specific items for menses and presence of PMS symptoms. During the 3-month study period, patients were asked to continue the diary record, in order to compare—at the end of the study period—headache frequency and duration with data obtained by previous headache diaries. Patients were asked to give subjective information about VAC efficacy on PMS by a score: 0 = no effect on PMS (absence of modification, or worsening effect); 1 = mild reduction on PMS (intensity and duration were reduced, symptomatic drugs were not yet needed, patients were slightly disabled); 2 = dramatic

reduction or total absence of PMS (symptoms disappeared/were very mild). This subjective information score about PMS was compared with that one resulting from diaries, discussed with the patient and eventually corrected.

### Statistic analysis

A repeated measure *t* test was used to assess differences in migraine frequency and duration (attacks and days per month) between the month before the start of the study and the third month of VAC assumption. Also, several binary logistic regressions were performed to find predictors of VAC effectiveness on migraine. The statistical analysis was performed by SPSS package for Windows (version 13).

### Classification of evidence

Our study provides Class IV evidence that VAC is helpful in migrainous women with PMS.

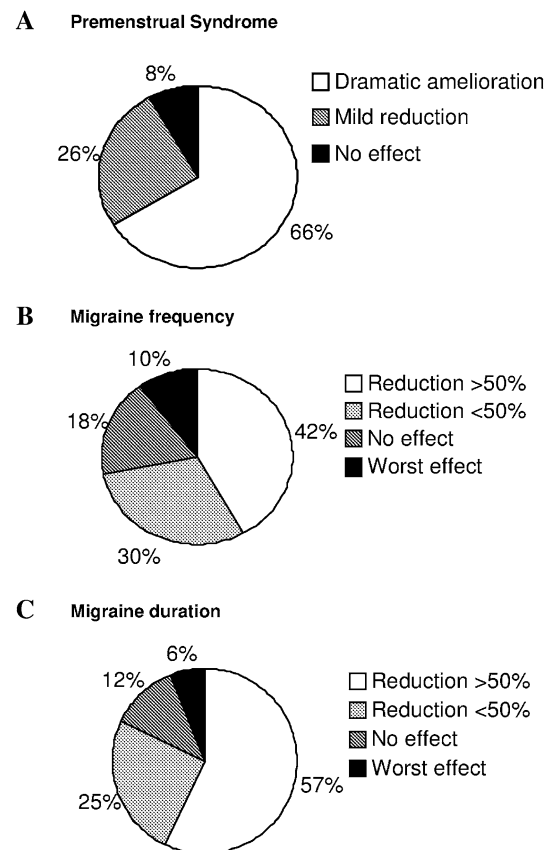
### Results

One hundred and seven women (mean age 35.58 years; range 18–50; SD = 8.48) were enrolled in the study. Among them, seven dropped out before the end of the 3-month study period. However, no major side effects were seen: one patient dropped out because she referred the onset of head pruritus; one patient reported a mild gastralgia; one patient the worsening of PMS; one patient the worsening of dysmenorrhoea; and three patients had a bad compliance to the study and did not respect the daily assumption of VAC.

The mean age of women who completed the study was 35.3 (range 18–50; SD 8.6). Before the treatment, the mean frequency of monthly attacks was 4.3 (range 2–8; SD 1.7), the mean number of monthly days with headache was 7.4 (range 2–18; SD 3.8). Forty-seven patients were in previous prophylactic treatment for migraine, not modified in the 4 months before the starting of the study nor during the study period, while 53 were drug free.

After the treatment with VAC at a daily dose of 40 mg, 66 patients out of 100 reported a dramatic subjective amelioration of PMS symptoms (score 2), 26 a mild amelioration (score 1), and 8 with no effect (score 0). About migraine frequency (attacks per months), 72 patients reported a reduction, 18 no modifications, and 10 a worsening effect; about migraine duration (days per month), a reduction was reported by 82 women, absence of influence by 12, and a worsening effect by 6. (Fig. 1). The mean frequency of monthly attacks, after the treatment, was reduced to 2.87 (range 0–9; SD 1.7), and the mean number of monthly days with headache decreased to 3.97 (range

0–15; SD 2.7). Reduction was significant both in term of attacks ( $t = 8.07$ ;  $p < 0.0001$ ) and days ( $t = 11.21$ ;  $p < 0.0001$ ) (Fig. 2). To assess whether VAC effect on headache was present also in the absence of a migraine prophylactic treatment, analysis was repeated both for the group already treated and for the group not in treatment. In the first group, mean monthly headache frequency before VAC admission was 4.51 (SD = 1.68), and mean monthly headache days 8.04 (SD = 3.86); after VAC treatment mean monthly headache frequency was 3.3 (SD = 1.79;  $t = 4.61$ ;  $p < 0.0001$ ), mean headache monthly days 4.66 (SD = 3.05;  $t = 7.78$ ;  $p < 0.0001$ ). For the group not in treatment, mean monthly headache frequency before VAC admission was 4.06 (SD = 1.73), mean monthly headache days were 6.7 (SD = 3.37); after VAC treatment mean monthly headache frequency was 2.49 (SD = 1.56;  $t = 6.92$ ;  $p < 0.0001$ ), mean monthly headache days 3.36 (SD = 2.15;  $t = 8$ ;  $p < 0.0001$ ). Women were categorised as “responders” to VAC in the presence of a reduction of headache of at least 50 % [22]. On the whole, 42 % of patients experienced a reduction in frequency of monthly attacks higher than 50 %, and 57 % of patients experienced a reduction in monthly days with headache higher than 50 %.



**Fig. 1** Effect of *Vitex agnus-castus* on PMS (a), migraine frequency (b), and headache duration (c)

Logistic regression analyses did not show any influence of patients' age, monthly number of headache attacks, monthly number of headache days, and ongoing prophylactic therapy for migraine on VAC effectiveness.

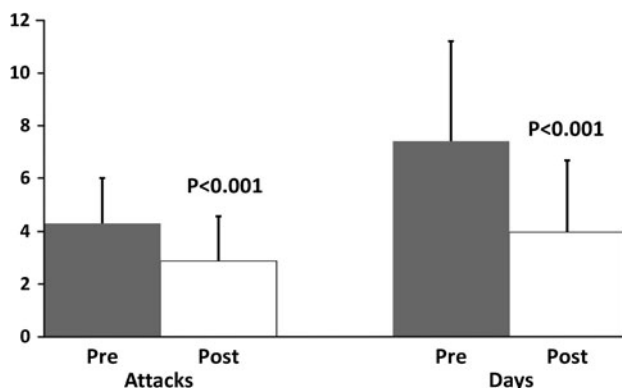
## Discussion

Our study seems to suggest an amelioration of migraine during PMS treatment with VAC.

Although the positive effect of VAC on PMS was already well known [12–15] and headache was previously suggested as a very usual feature of PMS [8], VAC effect on headache was never investigated either in patients with a headache only related to PMS or in migraineurs also affected by PMS. VAC resulted to be substantially well tolerated by migraineurs: only one patient reported head pruritus (fully reverted in a few days after VAC discontinuation), one reported reactivation of an already existing gastralgia (not necessarily related to VAC assumption), five reported the ineffectiveness, or a worsening effect on PMS and dysmenorrhoea, because of they did not complete the 3-month period of treatment and observation.

As it was not part of our endpoints, no specific and validated tools to assess PMS reduction have been used, as studies that analyse the effect of VAC on PMS already exist. Anyhow our results, based on patients' opinion and their diaries, suggest VAC effectiveness on PMS also in migrainous women.

Interestingly, in our patients, assumption of VAC would appear to positively influence frequencies and intensities not only of menstrual- or ovulation-related migraine attacks, but also attacks not apparently related to the menstrual cycle. This positive outcome seems not to be influenced by women's age, headache frequency or duration, or by the assumption of other drugs for migraine prophylaxis. Mechanism of action for VAC implies its agonist activity on sexual steroids, dopaminergic, and



**Fig. 2** Mean and SD of monthly headache attacks and monthly headache days before and after VAC treatment

opiate systems [23–27] but an anti-inflammatory and neuroprotective effect was also supposed for this compound [28]. VAC, a member of the verbenaceae family, has been used in human and animal medicine since ancient times. Its anti-inflammatory effect was reported around 400 BC by Hippocrates; its neuropsychiatric indications were firstly mentioned in Persian texts of the ninth and twelfth centuries. In the Middle Ages, VAC was used in Europe to suppress sexual urges and became a symbol of chastity (from this indication, popular names of “Chaste Tree” and “Chasteberry” are derived), but this effect was successively disputed, being also used to improve libido in both genders. However, thanks to the peppery taste of its dried fruit, it was also used as a pepper substitute by monks to control their libidinal tendencies (for this reason, it was also named “Monk’s pepper”). Traditionally VAC has been used to treat depression, sleep disorders, gynaecological complaints (e.g. dysmenorrhoea, endometriosis, PMS, menopausal disorders), lactation disorders, anxiety, acne, flatulence, and to suppress appetite.

Mainly this compound have pharmacological activities that work on the reproductive steroid, dopaminergic, and opiate systems and modulate inflammation [24–28], properties that seem of capital importance for treating migraine, as each one of these effects could act positively on it. In particular, the effect of ovarian hormones on migraine is well known and widely discussed by several authors: it is a matter of fact that migraine is 3 times more common in women of childbearing age, and maybe this is due to brain excitability modifications induced by sexual hormones fluctuations; these modifications could induce, for instance, the cortical spreading depression, starting migraine attack. Stabilisation of this hormonal activity could improve migraine [29].

In conclusions, our preliminary open-label study suggests that, when used in migrainous women in order to treat PMS, VAC seems to be safe and well tolerated and could improve preventative management of both menstrual-related and non-menstrual-related migraine headaches.

A double-blind controlled trial would be auspicated to confirm VAC efficacy on migraine, eventually also as an add-on therapy for women who received a non-satisfactory prophylactic treatment for their migraine comorbid with PMS.

**Conflict of interest** The authors declare that they have no conflicts of interest.

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