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Treatment of Premenstrual Syndrome with a Phytopharmaceutical Formulation Containing *Vitex agnus castus*

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ABSTRACT

A multicentric noninterventional trial (open study without control) to investigate the efficacy and tolerance of a drug in a large number of patients under routine medical conditions was performed for a new solid preparation from an extract of the fruit of *Vitex agnus castus* (VAC, *Vitex*, chaste tree, Chasteberry) in 1634 patients suffering from premenstrual syndrome (PMS). A specific questionnaire was developed for determining the effect of *Vitex* on psychic and somatic complaints, on the four characteristic PMS symptom complexes depression, anxiety, craving, and hyperhydration (DACH), and on single groups of symptoms. After a treatment period of three menstrual cycles 93% of patients reported a decrease in the number of symptoms or even cessation of PMS complaints. To a certain extent, this effect was observed within all symptom complexes and correlated with the global assessment of therapeutic efficacy. Whereas 85% of physicians rated it as good or very good, 81% of patients assessed their status after treatment as very much or much better. Analysis of frequency and severity of mastodynia as the predominant symptom revealed that complaints still present after 3 months of therapy were mostly less severe. Ninety-four percent of patients assessed the tolerance of *Vitex* treatment as good or very good. Adverse drug reactions were suspected by physicians in 1.2% of patients, but there were no serious adverse drug reactions. Hence, the risk/benefit ratio of the new *Vitex* preparation can be rated as very good, with significant efficacy for all aspects of the multifaceted and inhomogeneous clinical picture of PMS, with a safety profile comparable to other *Vitex* preparations.

INTRODUCTION

THE MENSTRUAL CYCLE REACTS sensitively to many influences on the regulative system of the central nervous structures (hypothalamus and pituitary gland) and the ovaries as peripheral target organs. Pathological changes in this sensitive system can cause a wide range of complaints and diseases, requiring an effective as well as a tolerable therapeutic strategy.

In this context, the premenstrual (tension) syndrome (PMS) is very important. PMS is characterized by psychic and somatic symptoms typically occurring in the second part of the female cycle and disappearing with the onset of or during menstrual bleeding.[1] Up to 150 different symptoms have been recorded as part of PMS. Because the multitude of heterogeneous symptoms can be attributed to the four subgroups, depression, anxiety, craving, and hyperhydration,[2,3]

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PMS may also be referred to as the DACH syndrome (for single symptoms of these subgroups, see Table 1).

According to the scientific literature, the prevalence of PMS is about 30%–40% in fertile women, and 5%–10% suffer from severe complaints.[4] A recent investigation involving students of pharmacy at Basel University ($n = 132$) revealed a prevalence of 70% regardless of the intake of oral contraceptives.[5]

The etiology of PMS has not been completely explained, and several mechanisms are being discussed[5]: estrogen and gestagen imbalance, deficiency of prostaglandins, essential fatty acids, vitamin B_6, serotonin, or other neurotransmitters, and hyperprolactinemia, especially where the predominant symptom is mastodynia.[4] Therefore, various therapeutic strategies have been employed, such as hormone therapies, substitution of essential fatty acids, and the use of pyridoxine and psychiatric drugs, but either benefits are controversial,[1,5] or side effects limit the use of these therapies.

Thus, there is a need for a treatment that alleviates both somatic and psychic complaints and that has a good tolerance. In the last decades, phytopharmaceutic preparations containing *Vitex agnus castus* (VAC) extracts have been used. *Vitex* (chaste tree, chasteberry) is a bushy plant native to the Mediterranean countries and Asia. Extracts from its fruit (*Agni casti fructus*) have been used for treating gynecological complaints since Greek antiquity.[6] At present, scientifically developed and well-accepted pharmaceuticals contain such extracts as the active ingredient. The German monograph on *Vitex* documents three indications, PMS, mastodynia, and menstrual rhythm anomalies, that can be treated with *Vitex*.[7]

The mode of action of *Vitex* is not completely understood.[6] Presumably, different mechanisms contribute to the therapeutic effects, one of which is a decrease in prolactin via dopamine-D2 receptor binding at the pituitary gland.[8–10] Furthermore, binding affinities of a special *Vitex* extract to opioid receptors, the histamine H_1 receptor, and estrogen receptors were observed recently.[5]

There is clinical evidence for the efficacy of various *Vitex* extracts. With respect to the symptom rhythm anomalies, the superiority of a *Vitex* extract versus placebo was demonstrated in a 3-month randomized trial.[11] Effects on the symptom, mastodynia, were shown in a randomized placebo-controlled trial.[10] Therapeutic effects for PMS were documented in drug-monitoring studies (reviewed in ref. 5). In a controlled study comparing 3 months of therapy with either vitamin

Table 1. PMS Symptoms at Beginning and After *Vitex* Treatment

	Initial visit		*Final visit*	
Symptoms	*No. of patients*	*%*	*No. of patients*	*%*
Psychic complaints	1335	81.7[a]	420	25.7[A]
Depression	772	47.2[a]	213	13.0[A]
Depression, frequent weeping	469	28.7[a]	83	5.1[A]
Dyscoimesis (problems in getting to sleep)	322	19.7[a]	87	5.3[A]
Dysphylaxia (problems in sleeping through)	292	17.9[a]	87	5.3[A]
Anxiety	1165	71.3[a]	307	18.8[A]
Nervousness, agressiveness, irritability, mood swings, impatience, increased excitability, anxiety	1165	71.3[a]	307	18.8[A]
Somatic complaints	1599	97.7[a]	815	49.9[A]
Craving	942	57.6[a]	269	16.5[A]
Headache/migraine, vertigo, tiredness	875	53.5[a]	242	14.8[A]
Tachycardia	218	13.3[a]	43	2.6[A]
Hyperhydration	1521	93.1[a]	697	42.7[A]
Pain/tension in the mammae	1333	81.6[a]	480	29.4[A]
Sensation of fullness, flatulence, constipation, nausea, vomiting	652	39.9[a]	137	8.4[A]
Bloatedness, edema	273	16.7[a]	105	6.4[A]
Short-term weight gain corresponding with menstruation	620	37.9[a]	124	7.6[A]
Back and/or joint pain	476	29.1[a]	167	10.2[A]
PMS in total	1634	100.0	954	58.4[A]

[a,A]Statistically significant differences between [a]the first and [A]the second values ($p < 0.001$, Wilcoxon test).

Table 2. Severity of Mastodynia at Beginning and After *Vitex* Treatment

Symptoms	*Degree of severity*	*Initial visit affected patients (%)*	*Final visit affected patients (%)*
No mastodynia	0	18.3[a]	70.4[A]
Tension in mammae	+	40.1[a]	23.3[A]
Tenderness to touch	++	30.3[a]	4.5[A]
Spontaneous pain in mammae	+++	11.3[a]	1.8[A]

[a,A]Statistically significant differences between the corresponding value of [a]the first and [A]the second visit ($p < 0.001$, Wilcoxon test).

B_6 (200 mg/day) or *Vitex* (40 mg drug/day) the efficacy of *Vitex* in the treatment of PMS was confirmed.[12]

Because the origin of the plant material and the extraction procedure are decisive factors in the efficacy and tolerance of the phytopharmaceutical,[6] we initiated this study to review these parameters for a new *Vitex* preparation under routine medical conditions. The major objective of such a noninterventional trial is to gather medical experience on the efficacy and tolerance of an established product in a systematic and scientifically reliable manner during routine medical work in a doctor's practice. The therapeutic effect of the *Vitex* preparation on any of the four classic PMS complexes (DACH syndrome) and any other typical symptoms was assessed. Mastodynia especially, as the most common PMS symptom, was analyzed for frequency and severity.

MATERIALS AND METHODS

In a multicenter noninterventional trial, data on 1634 patients were obtained by 857 gynecologists in Germany to assess information about the efficacy and safety of a new *Vitex* preparation (Femicur® capsules, Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany) (one capsule containing 1.6–3.0 mg dried extract of *Agni casti fructus* [6.7–12.5:1], corresponding to 20 mg drug) used in daily practice. The investigators were informed about the characteristics of this phytopharmaceutical and its directed use, including the recommended dosage (one capsule twice daily). Suffering from PMS was the only inclusion criterion. Pregnant patients were excluded from treatment, but no further instructions concerning the therapy were given.

When Femicur® was given as therapy of PMS, the investigator was asked to fill in one questionnaire at the start of therapy and another one after a period of three menstrual cycles under therapy. In accordance with the prospectively implemented study protocol, these questionnaires were used by all investigators. The questionnaires consisted of items questioning the efficacy and tolerance of the treatment. They were filled in by the investigator after interviewing the patient.

Efficacy

The investigator documented the occurrence of typical PMS symptoms in the beginning and at the end of therapy. The decrease in frequency at which symptoms were occurring was used as a measure of efficacy (Table 1). Mastodynia, as the most prominent symptom of PMS, was documented qualitatively and quantitatively (Table 2).

The global efficacy was rated by the investigator on a four-category scale (very good efficacy to no efficacy) based on an interview after 3 months of treatment. Each patient assessed her global improvement according to the Clinical Global Impression Scale[13] (CGI 2), using a scale with seven categories (very much improved to very much worse).

Table 3. Reasons for Premature Termination of *Vitex* Treatment

Main reason for termination	*No. of patients*	*% of valid cases*
Insufficient improvement	42	2.6
Adverse event	18	1.1
Total recovery	17	1.0
Substantial improvement	16	1.0
Further reasons	21	1.3
Pregnancy	12	0.8
No data available	5	0.3

Tolerance

Tolerance was assessed by the patient on a four category scale (very good to bad), and adverse events were recorded. Data were entered into a database and analyzed using the statistical software WinSTAT® 3.1 (Kalmia Co. Inc., Cambridge, MA).

The conduct and analysis of this trial followed the recommendations on the conduct of noninterventional trials drawn up by the German Society for Medical Informatics, Biometry and Epidemiology (GMDS) at the instigation of the German Federal Institute for Drugs and Medical Devices (BfArM).[14]

RESULTS

Questionnaires were completed for 1698 patients, and 1634 were suitable for analysis. Thirty-one patients enrolled initially did not return for the second interview and gave no reason, 18 patients were excluded from the efficacy analysis because they did not suffer from PMS, 3 questionnaires showed a severe lack of relevant information, and in 12 cases, the questionnaires were returned after closure of the database. Among the valid cases, 119 patients (7%) had terminated the treatment prematurely (Table 3).

The 1634 patients in the valid-case population had a mean age of 35.8 ± 8.7 years, a height of 167.0 ± 5.5 cm, and a body mass index (BMI) of 23.1 ± 3.2. They had suffered from PMS for 151 ± 179 weeks with a mean of 4 ± 2 different symptoms and 9 ± 4 days with PMS complaints per menstrual cycle.

The efficacy and tolerance of *Vitex* treatment were evaluated after 99 ± 22 days of treatment.

Efficacy

Forty-two percent of patients reported that they were no longer suffering from PMS, 51% showed a decrease in symptoms, and 1% experienced an increase in the number of symptoms. In 6% of patients, the frequency of symptoms did not change. Table 1 shows details of the frequency of the different groups of PMS symptoms and the DACH complexes before and after treatment. Patients still suffering from PMS reported complaints on 5 ± 3 days (before therapy 9 ± 4 days) with 2 ± 1 different symptoms (before therapy 4 ± 2) per menstrual cycle. The decrease under therapy was statistically significant for both parameters ($p < 0.001$, paired samples *t*-test, Wilcoxon test). Mastodynia was the most frequent symptom in this trial. With treatment, its frequency decreased, and the severity was reduced as well (Table 2).

The results of assessment of the efficacy of treatment are shown in Figure 1. A clear improvement was assessed by 80% of the patients, and 86% of the physicians documented a pronounced efficacy.

Tolerance

In the patients' self-assessment, the tolerance was described as good or very good in 94% of

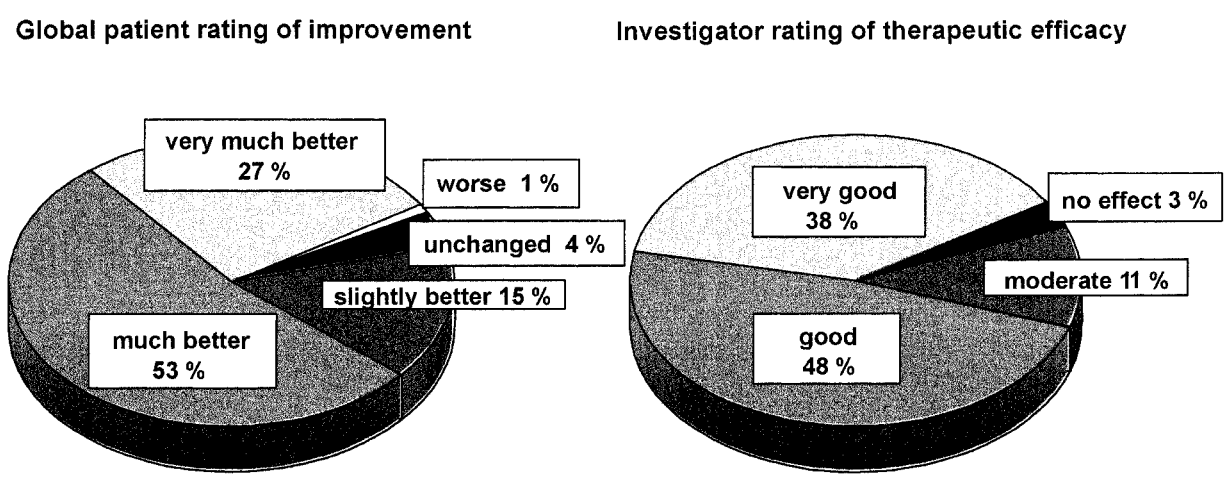

FIG. 1. Assessment of efficacy of treatment with *Vitex*.

cases (Fig. 2). For the total population of 1698 patients, 45 adverse events or symptoms were documented in 37 patients (2%) and none were serious. In 20 patients (1%) with 23 adverse events, a correlation with the intake of *Vitex* was assumed by the investigators. Table 4 shows details about the nature of these suspected adverse drug reactions.

During the period of treatment with *Vitex*, 23 patients became pregnant, and in 12 patients the treatment was terminated because of the pregnancy.

Compliance

In accordance with the German monograph, 90% of the investigators had prescribed a daily dosage of extract corresponding to 40 mg of *Agni casti fructus*. Patient compliance, as monitored by the investigators, was 98%.

DISCUSSION

The efficacy of *Vitex* in menstrual disorders and its good tolerance have been demonstrated in several trials.[6,9–12] The objective of this noninterventional trial was to prove the efficacy and safety in daily medical practice of a new *Vitex* preparation in patients with PMS. The approach was to differentiate between the different symptom complexes of PMS. A pronounced psychological aspect is characteristic of this syndrome.[15,16] This is reflected by the considerable decrease in the number of patients with psychic complaints after a mean treatment period of 3 months, exceeding the decrease in somatic symptoms, which itself was significant. More than 40% of all patients reported a complete cessation of all PMS complaints.

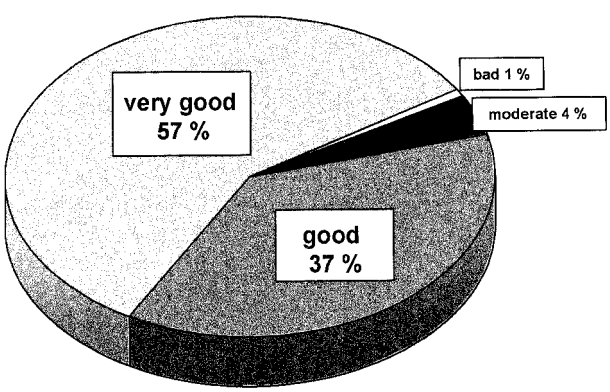

FIG. 2. Assessment of tolerance of treatment with *Vitex* (19% of patients: no statement).

TABLE 4. SUSPECTED ADVERSE DRUG REACTIONS

Suspected adverse drug reactions	N	%
Symptoms of skin, mucosa, integumentary appendage (itching, allergic reaction, vesicles, eczema, urticaria, acne, hair loss)	13	0.8
Symptoms of gastrointestinal tract (nausea, vomiting, diarrhea, pain in the stomach, tympanites)	6	0.4
Nosebleeding	1	<0.1
Edema	1	<0.1
Vertigo	1	<0.1
Spotting	1	<0.1

The decrease in anxiety symptoms was remarkably high, supporting the opinion that the psychological aspect of PMS must not be neglected. The occurrence of hyperhydration is the most variable and persistent symptom. After 3 months of treatment, >40% of patients still suffered from complaints of hyperhydration, but data on the mean number of symptoms and days with PMS complaints per menstrual cycle show that although the complaints did not cease entirely, the severity had diminished during the treatment phase. The qualitative record of mastodynia, the main symptom not only of the hyperhydration complex but of PMS in general,[10] supports this view. Although 30% of the women still complained about mastodynia after *Vitex* treatment, most of them reported that the complaints were clearly of lower intensity.

In 93% of the documented cases, the number of PMS symptoms decreased, and 95% of the patients experienced an improvement, whereas physicians assessed the therapeutic efficacy in 96% of the cases as at least moderate. This good efficacy is accompanied by equally good drug safety. The global assessment of tolerance—only 1% of patients rated it as bad—is supported by the low rate of suspected adverse drug reactions documented by the investigators for 1% of the women. These adverse events affected mainly the gastrointestinal tract, the skin, and the integumentary system. No data beyond the current knowledge on the safety of *Vitex* treatment were obtained.[6,17]

Data from this trial support the occasionally described restoration of fertility by *Vitex* treatment.[6,18] No woman was pregnant at the start of *Vitex* therapy, and 19 of the 23 women who conceived while on *Vitex* treatment belonged to the group of 126 women (8%) who had been to date unsuccessful at becoming pregnant. This observation may be explained by the effect of *Vitex* on corpus luteum insufficiency.[11]

CONCLUSIONS

A positive risk/benefit ratio exists for this *Vitex* preparation (Femicur®) in the treatment of PMS. In addition, this investigation examined the efficacy of *Vitex* in more detail by differentiating between characteristic PMS symptoms and the four DACH complexes. *Vitex* was proven to be effective with respect to all psychic and somatic symptoms of the heterogeneous and multifaceted PMS.

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