REVIEW ARTICLE

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Vitex agnus castus
A Systematic Review of Adverse Events

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Contents

Abstract

Vitex agnus castus L. (VAC) [Verbenaceae] is a deciduous shrub that is native to Mediterranean Europe and Central Asia. Traditionally, VAC fruit extract has been used in the treatment of many female conditions, including menstrual disorders (amenorrhoea, dysmenorrhoea), premenstrual syndrome (PMS), corpus luteum insufficiency, hyperprolactinaemia, infertility, acne, menopause and disrupted lactation. The German Commission E has approved the use of VAC for irregularities of the menstrual cycle, premenstrual disturbances and mastodynia. Clinical reviews are available for the efficacy of VAC in PMS, cycle disorders, hyperprolactinaemia and mastalgia, but so far no systematic review has been published on adverse events or drug interactions associated with VAC. Therefore, this review was conducted to evaluate all the available human safety data of VAC monopreparations.

Literature searches were conducted in six electronic databases, in references lists of all identified papers and in departmental files. Data from spontaneous reporting schemes of the WHO and national drug safety bodies were also included. Twelve manufacturers of VAC-containing preparations and five herbal-

ist organisations were contacted for additional information. No language restrictions were imposed. Combination preparations including VAC or homeopathic preparations of VAC were excluded. Data extraction of key data from all articles reporting adverse events or interactions was performed independently by at least two reviewers, regardless of study design.

Data from clinical trials, postmarketing surveillance studies, surveys, spontaneous reporting schemes, manufacturers and herbalist organisations indicate that the adverse events following VAC treatment are mild and reversible. The most frequent adverse events are nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus and erythematous rash. No drug interactions were reported. Use of VAC should be avoided during pregnancy or lactation. Theoretically, VAC might also interfere with dopaminergic antagonists.

Although further rigorous studies are needed to assess the safety of VAC, the data available seem to indicate that VAC is a safe herbal medicine.

Vitex agnus castus L. (VAC) [Verbenaceae], also known as chaste tree, chasteberry and monk's pepper, is a deciduous shrub that is native to Mediterranean Europe and Central Asia. It has been used for female reproductive disorders since ancient Greek and Roman times. In the 4th century B.C., Hippocrates recommended the plant for injuries, inflammation and swelling of the spleen. VAC is also mentioned in the works of Dioscorides and Theophrast.[1]

The name agnus castus derives from the Latin words 'castitas' (chastity) and 'agnus' (lamb); it is also called 'chaste tree', which refers to its ability to decrease sexual desire and promote chastity in women and celibacy in monks. Another common name, 'monk's pepper', originates from its use by monks as a spice in cooking.

Traditionally, VAC has been used by practitioners of phytotherapy in the treatment of many female conditions, including menstrual disorders (amenorrhoea, dysmenorrhoea), premenstrual syndrome (PMS), corpus luteum insufficiency, hyperprolactinaemia, infertility, acne, menopause and disrupted lactation.[2] In popular medicine, VAC is also considered to be an emmenagogue, vulnerary, carminative, lactagogue, anthelmintic and anti-inflammatory.[3] The German Commission E has approved the use of VAC for irregularities of the menstrual cycle, premenstrual disturbances and mastodynia.[4]

In Europe, the parts used for medicinal purposes are the ripe dried fruit and extracts/concentrates of this part of the plant. Its constituents are flavonoids (casticin, isovitexin, orientin), iridoids (aucubin, agnuside, eurostide), volatile oils (monoterpenes and sesquiterpenes), linoleic acid and a bitter principle called castine.[5,6] The whole plant extract is considered necessary for the therapeutic action.[7] The authenticity of VAC is usually measured by its agnuside content.[7]

VAC is believed to act on the hypothalamus and pituitary gland, thus indirectly altering the balance of sex hormones. The mode of action of VAC is not completely understood and several mechanisms have been considered. The most probable is an interaction with dopaminergic receptors in the anterior pituitary gland with a subsequent reduction of prolactin secretion, derived from evidence from human *in vivo* studies.[8-10] Prolactin is produced by the anterior pituitary gland and plays an important role in a variety of reproductive functions;[11] levels rise naturally during pregnancy to induce the development of the mammary glands and to stimulate milk production. Raised levels of prolactin in non-lactating women are associated with female disorders, such as cyclic breast tenderness, menstrual abnormalities, absence of ovulation and some symptoms of PMS.[11] Other reviews are available for the efficacy of VAC in PMS, cycle disorders, hyperprolactinaemia and mastalgia.[2,12-15]

To our knowledge, no systematic review is available on adverse events and drug interactions associated with VAC. Therefore, the aim of this review was to evaluate all the available human safety data of VAC monopreparations.

1. Search Methodology

Systematic literature searches were performed in September 2004 in the following electronic databases: Medline, Amed, Cinahl, Embase, Psycinfo and The Cochrane Library. The search terms were 'vitex agnus castus', 'agneau chaste', 'agnus castus', 'chasteberry', 'gatillier', 'hemp tree', 'keuschlamm', 'monk's pepper', 'vitex', 'agnolyt', 'agnucaston', 'femicur', 'agnumens', 'castufemin', 'gynocastus', 'strotan', 'agnufemil', 'cefanorm', 'femicur', 'kapslan', 'hewekliman' and 'kytta femin'. No language restrictions were imposed. Further relevant papers were located by hand-searching the reference lists of all papers and searching departmental files. Data were also requested from the following spontaneous reporting schemes: Adverse Drug Reactions Advisory Committee (ADRAC), Australia; Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Germany; Medicine and Healthcare Products Regulatory Agency (MHRA), UK; and the WHO Collaborating Centre for International Drug Monitoring, Sweden. Twelve manufacturers of VAC preparations, identified from standard references texts,[16,17] were contacted and asked to supply any information about adverse events or drug interactions of VAC. In addition, five herbalist organisations (National Institute of Medical Herbalists, England; College of Practitioners of Phytotherapy, England; British Herbal Medicine Association, England; International Register of Consultant Herbalists and Homeopaths, Wales; European Herbal Practitioners Association, England) were asked for any additional information. All data from clinical trials, case reports, case series, surveys and postmarketing surveillance studies were included in this review.

Only human studies assessing monopreparations of VAC were included. Data from VAC in combination with other herbs or homeopathic preparations of VAC, as well as animal and *in vitro* investigations, were excluded. Where dual publications existed, only one report (the more detailed) was admitted. All sources of information obtained were read and evaluated by one reviewer and independently checked by at least one additional author.

Data were extracted according to predefined criteria (patient population, preparation and dose, number and type of adverse events reported). No formal assessment of the statistics of the primary data was made.

2. Results of Literature Search

Eighty-two articles were located. Of these, 49 articles were excluded because they were either performed with VAC in combination with other compounds (n = 24), did not include original data or were duplicate publications (n = 25). The remaining 33 studies were included in this review (figure 1). All except two studies involved women.

2.1 Data from Clinical Trials

2.1.1 Randomised Controlled Trials

Five randomised controlled trials were located;[18-22] three of these were placebo controlled[18-20] and the others compared the effect of VAC with that of other active compounds[21,22] (table I).

Of the three randomised placebo-controlled studies, only one[18] reported adverse events following VAC treatment. This was a double-blind, placebo-controlled trial that was performed for three menstrual cycles in 170 women with PMS. Patients in the VAC group (n = 86) received one VAC fruit extract Ze 440 20mg tablet daily (Zeller AG, Switzerland; 60% ethanol (m/m), extract ratio 6–12 **:** 1, standardised for casticin). Four adverse events (4.7%) were reported in the VAC group (acne, multiple abscesses, inter-menstrual bleeding, urticaria) and three (3.6%) in the placebo group (acne, early menstrual period, gastric upset). Each event was reported only once and resolved without treatment discontinuation.

Another randomised, double-blind, placebo-controlled study[19] included 52 women (37 complete cases were available for analysis: VAC = 17, placebo = 20) with luteal phase defects as a result of hyperprolactinaemia. The study medication (Strotan® **1** capsules, Pharma Stroschein GmbH, Germany; one capsule corresponding to 20mg of extract) was administered for 3 months. There were

1 The use of trade names is for product identification purposes only and does not imply endorsement.

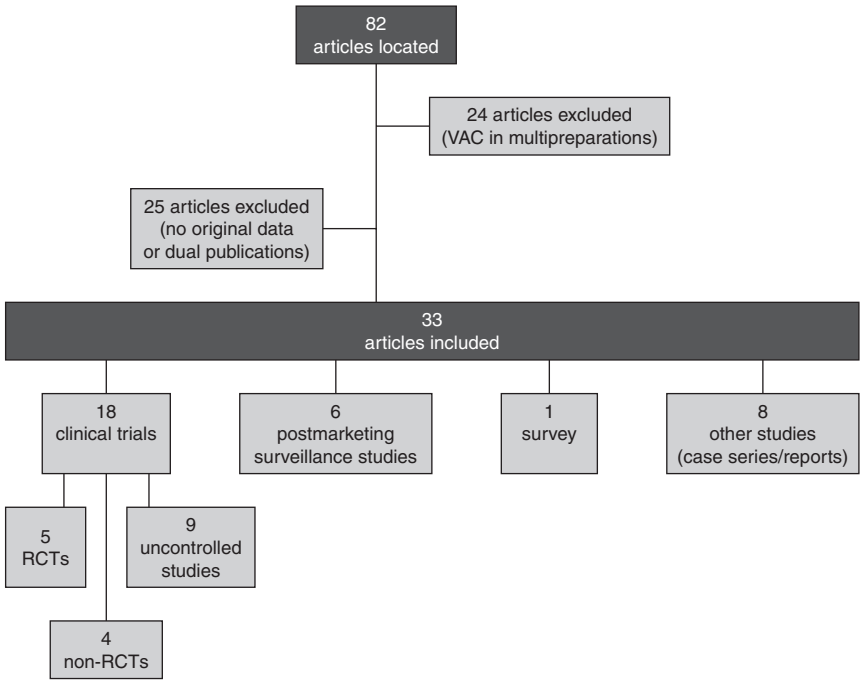

Fig. 1. Flow chart of studies. **RCT** = randomised controlled trial; **VAC** = *Vitex agnus castus*.

no adverse events and two women in the VAC group became pregnant.

In the double-blind study by Turner and Mills,[20] 600 women with PMS were randomly allocated to receive VAC (two tablets of powdered Vitex three times daily; one tablet corresponding to 300mg of powdered VAC) or placebo for 3 months. 217 women (VAC = 105, placebo = 112) completed the treatment. No mention of adverse events or tolerability was made.

In a multicentre, randomised controlled trial,[21] the efficacy and tolerability of Agnolyt® capsules (MADAUS, Germany; one capsule contains dried extract of VAC fruit [9.58–11, 5 : 1] 3.5–4.2mg) were determined versus pyridoxine in women with PMS. 175 women were randomised to receive VAC treatment (one capsule of Agnolyt® plus one capsule of placebo) or pyridoxine treatment (one capsule of placebo twice daily on days 1–15 of the cycle and one capsule of pyridoxine hydrochloride 100mg twice daily on days 16–35 of the cycle) for three menstrual cycles. At the end of the study, complete data were obtained from 127 patients (VAC = 61, pyridoxine = 66). Forty-eight patients (24 in each group) were excluded from both the intent-to-treat and the per-protocol analysis because of protocol violations (invalid or missing symptom scores or an excessively high score on the depression scale giving rise to the possibility of suspected depression). Adverse events were reported in 12 women of the VAC group and in 5 of the pyridoxine group. Serious adverse events were not observed, but there was a premature discontinuation of the treatment as a result of the adverse events by nine patients: five in the VAC group (allergic rashes [2], persistent gastroenteritis [1], nausea [1], acneiform facial inflammation [1]) and four in the pyridoxine group (lump in the throat [1], abdominal discomfort [1], recurrence of a known ulcerative colitis [1], persistent bleeding of unknown origin [1]). In the case of one patient in the VAC group and two patients in the pyridoxine group, participation in the study was terminated at the patients' request or because of emotional stress. Although women wishing to conceive were excluded from the study, five women from the VAC group became pregnant during the trial.

Table I. Adverse events of *Vitex agnus castus* (VAC) reported in clinical studies

Study	No. of study participants	Preparation/ daily dose	Treatment duration	Adverse events
RCTs				
Turner and Mills[20]	217	VAC powdered 1800mg	3mo	Not reported
Milewicz et al.[19]	37	Strotan®[a] 1 capsule	3mo	Adverse events were not observed
Lauritzen et al.[21]	127	Agnolyt®[b] 1 capsule	3mc	VAC group: 12 patients reported adverse events and 5 withdrew (nausea [1], persistent gastroenteritis [1], allergic rashes [2], acneiform facial inflammation [1]) Control (pyridoxine) group: 5 patients reported adverse events and 4 withdrew (lump in the throat [1], abdominal discomfort [1], ulcerative colitis [1], persistent bleeding [1])
Schellenberg[18]	170	VAC extract Ze 440[c] 20mg	3mc	VAC group: inter-menstrual bleeding (1), acne (1), multiple abscesses (1), urticaria (1) Control (placebo) group: acne (1), early menstrual period (1), gastric upset (1)
Atmaca et al.[22]	41	VAC extract 20–40mg	8wk	VAC group: 8 patients reported 16 adverse events and 1 withdrew; most frequent adverse events: headache (4), nausea (5) Control (fluoxetine) group: 9 patients reported 20 adverse events and 2 withdrew; most frequent adverse events: headache (4), nausea (6), insomnia (3)
Non-RCTs				
Bautze[23]	200	Agnolyt®[d] 90 drops	Not specified	Not reported
Mohr[24]	817	Agnolyt®[d] 90 drops	3mo	15 patients reported itching/exanthema, some women reported earlier menstrual period
Giss and Rothenburg[25]	161 (men and women)	Agnolyt®[d] 40 drops (4–6 wk) then 30 drops (1–2 y)	≥3mo	Not reported
Merz et al.[26]	20 (men)	VAC extract (BP 1095E1) 3 increasing doses (120mg, 240mg, 480mg)	14d for each dose	Skin reaction (1); vegetative disorders (dry mouth, disturbed sleep, tachycardia) [10]; gastrointestinal disorders (nausea, vomiting, feeling of pressure in the epigastric region) [6]; disturbed perception (1), slight confusion (1), slight activated states (1), headache (1), itching in the roof of the mouth and in the nose (1)
Uncontrolled studies				
Kayser and Istanbulluoglu[27]	51	Agnolyt®[d] 45 drops	Not specified	Adverse events were not observed
Probst and Roth[28]	57	Agnolyt®[d] (dose variable)	Variable	Not reported
Roth[29]	57	Agnolyt®[d] min. 45 drops	2wk to 3mo	Adverse events were not observed
Bleier[30]	126	Agnolyt®[d] 45 drops	≥4wk	Low abdominal and back pain (1), premenstrual tension (1), low abdominal pain and increased vaginal discharge (1), glandular hyperplasia (1)
Coeugniet et al.[31]	36	Agnolyt®[d] 40 drops	3mo	Adverse events were not observed

Continued next page

Table I. Contd

Study	No. of study participants	Preparation/ daily dose	Treatment duration	Adverse events
Propping and Katzorke[32]	18	Agnolyt®[d] 40 drops	3mo	Adverse events were not observed
Propping et al.[33]	45	Agnolyt®[d] 40 drops	3mo	Not reported
Neumann-Kühnelt et al.[34]	33	Agnus castus 40 drops	5mo	Not reported
Berger et al.[35]	43	VAC extract Ze 440[c] 20mg	3mc	Most frequent adverse events: acne (7), headache (6), spotting (5), gastrointestinal disturbances (5). One patient withdrew because of fatigue and headache 4 days after starting treatment

a Strotan® capsules, Pharma Stroschein Germany; one capsule corresponding to 20mg of extract.

b Agnolyt® capsules, MADAUS Germany; one capsule contains dried extract of VAC fruit [9.58–11,5 : 1] 3.5–4.2mg.

c VAC fruit extract Ze 440, Zeller AG Switzerland; 60% ethanol (m/m), extract ratio 6–12 : 1, standardised for casticin.

d Agnolyt® tincture, MADAUS Germany; 100g of tincture [1 : 5] contains 9g of VAC.

mc = menstrual cycles; **RCT** = randomised controlled trial.

A further randomised single-blind trial[22] compared the efficacy of VAC extract with fluoxetine in women experiencing premenstrual dysphoric disorder. The study involved 41 patients (VAC = 20, fluoxetine = 21) who received VAC extract or fluoxetine (daily dose range 20–40mg for each) for 8 weeks. Thirty-six adverse events were reported: 16 were reported by eight patients treated with VAC and 20 were reported by nine patients in the fluoxetine group. There was a withdrawal from the study because of adverse events in one patient from the VAC group and in two patients from the fluoxetine group. The most frequent adverse events were nausea and headache for VAC treatment, and nausea, headache and insomnia for fluoxetine treatment. The severity of adverse events was mild in all patients.

2.1.2 Non-Randomised Clinical Trials

Four non-randomised clinical trials were located (table I).[23-26] In a study assessing tolerability and dose-response effects on prolactin secretion, Merz et al.[26] studied 20 healthy men in an intra-individual comparison of a special VAC extract (BP1095E1) and placebo. All the men received the following medication sequence: placebo, VAC dosage A (120 mg/day), VAC dosage B (240 mg/day) and VAC dosage C (480 mg/day). Each administration lasted 14 days and there was a wash-out period of at least 1 week between each treatment. The administered doses were 3–12 times higher than the recommended dosage usually used by women. Adverse events were reported in 18 men (dosage A = seven men; dosage B = three men; dosage C = eight men). There were single cases of the following adverse effects: disturbed perception, slight confusion, slight activated states, headache, itching in the roof of the mouth and in the nose; ten cases of vegetative disorders (dry mouth, disturbed sleep, tachycardia), six cases of gastrointestinal disorders (nausea, vomiting, feeling of pressure in the epigastric region) and three cases of skin reactions. The correlation with VAC treatment was judged as 'uncertain' in the majority of cases. No dependency or intensification of symptoms was exhibited with increasing dose. No effects on liver enzyme levels, blood pressure or heart rate were observed compared with placebo.

A comparative study by Giss and Rothenburg[25] involved 161 patients with acne. 118 men and women were treated with Agnolyt® tincture (100g of tincture [1 : 5] contains 9g of VAC), 40 drops daily for 4–6 weeks then 30 drops daily for 1–2 years, and 43 did not receive treatment. All patients were treated for a minimum of 3 months. No mention of adverse events was made.

In another study,[23] the effect of VAC on breastfeeding was studied. The study involved 200 women: 100 were treated with Agnolyt® tincture (30 drops three times daily) and 100 did not receive any medication. Treatment duration was not specified. No mention of adverse events was evident in this paper.

Another study[24] examined the effect of Agnolyt® tincture in lactating women. This study was conducted in 817 women: 353 women were treated with VAC, 102 with thiamine (vitamin B_1) and 362 received no treatment. There were 15 cases of pruritus, exanthema and urticaria, and some cases of early menstrual period.

2.1.3 Uncontrolled Studies

Nine uncontrolled clinical trials were located (table I).[27-35] In a prospective and multicentre study,[35] the efficacy and safety of a VAC extract were evaluated. This trial involved 50 women with PMS treated with VAC extract Ze 440 (Zeller AG, Switzerland), one tablet (20mg of total extract) daily for three menstrual cycles. Data were completed for 43 patients. Twenty patients reported 37 adverse events. The most frequent events were acne (7), headache (6), menstrual spotting (5) and gastrointestinal disturbances (5). One patient withdrew because of fatigue and headache 4 days after starting treatment.

In another uncontrolled study,[30] 126 women with menstrual disorders (oligomenorrhoea, polymenorrhoea and amenorrhoea) were treated for a minimum of 4 weeks with Agnolyt® tincture (15 drops three times daily). Adverse events were observed in four patients. Increased menstrual flow, glandular hyperplasia, premenstrual tension and back pain were reported once; low abdominal pain was reported in two patients.

In four studies,[27,29,31,32] no adverse events were observed with VAC treatment, and in three studies[28,33,34] there was no mention of adverse events.

2.2 Data from Postmarketing Surveillance Studies

We identified six postmarketing surveillance studies[36-41] (table II). The study by Feldmann et al.[36] involved 1571 women with corpus luteum insufficiency and symptoms of PMS. The patients received an average of 41 drops daily of Agnolyt® tincture for about 135 days. Adverse events were reported in 30 patients (1.9%); nausea, stomach disturbances and diarrhoea were observed in 12 patients; single cases of allergy, weight increase, heartburn, hypermenorrhoea and dizziness were reported, and no specific information on adverse events was relayed for the remaining 13 patients. Sixteen patients (1.0%) withdrew from the study because of adverse events and 69 (4.4%) because of treatment failure.

Loch et al.[37] described the results of two postmarketing surveillance studies involving 2447 women with PMS and bleeding abnormalities. The women were treated with Agnolyt® tincture. The dosage was 42 drops daily and the treatment duration was on average 153 days. Fifty-six patients (2.3%) reported the following adverse events: unwellness, dizziness, heartburn, hypermenorrhoea, pruritus, colpitis, increased eye pressure, palpitations and constipation were each reported once; allergy, acne, exanthema and skin redness were each reported twice; headache and weight gain were each reported three times; diarrhoea, stomach disturbances and luteal phase defects were each reported four times; and nausea was reported eight times. Twenty-four patients (1.0%) dropped out because of adverse events.

In a study by Propping et al.,[38] 1592 women who were experiencing menstrual disorders or PMS were treated with Agnolyt® tincture (mean daily dose of 43 drops) and monitored for 6 months. Adverse events were reported in 39 patients (2.4%). The most frequent events were nausea (7), change in menstruation duration (5), weight gain (4), acne, exanthema and headache (3), stomach disturbances and skin redness (2). Fourteen patients (0.9%) terminated the treatment because of adverse events.

Table II. Adverse events of *Vitex agnus castus* (VAC) reported in postmarketing surveillance studies

Study	No. of study participants	Preparation/ daily dose	Treatment duration	Adverse events
Feldmann et al.[36]	1571	Agnolyt®[a] 41 drops (average)	135d (average)	Nausea, stomach disturbances, diarrhoea (12 cases); allergy, weight increase, heartburn, hypermenorrhoea, dizziness (1 case); no information (13 cases); 16 patients (1%) withdrew because of adverse events
Loch et al.[37]	2447	Agnolyt®[a] 42 drops (average)	153d (average)	Nausea (8), allergy (2), diarrhoea (4), unwell (1), weight gain (3), dizziness (1), heartburn (1), hypermenorrhoea (1), stomach disturbances (4), exanthema (2), skin redness (2), headache (3), colpitis (1), increased eye pressure (1), palpitations (1), constipation (1), acne (2), luteal phase defects (4), pruritus (1); no information (12); 24 patients (1%) withdrew because of adverse events
Propping et al.[38]	1592	Agnolyt®[a] 43 drops (average)	6mo	Most frequent adverse events: nausea (7), change in menstruation duration (5), weight gain (4), acne, exanthema and headache (3), stomach disturbances and skin redness (2); 14 patients (0.9%) withdrew because of adverse events
Dittmar et al.[39]	1542	Agnolyt®[a] 42 drops (average)	166d (average)	Nausea (5), allergy (1), diarrhoea (2), weight gain (1), dizziness (1), heartburn (1), hypermenorrhoea (1), stomach disturbances (3), luteal phase abnormalities (2), pruritus (1), redness of skin (2), alopecia (1), acne (3), palpitations (1), no information (7); 17 patients (1.1%) withdrew because of adverse events
Peters-Welte and Albrecht[40]	551	Agnolyt®[a] 40 drops	1wk to 19mc	Nausea (7), stomach or gallbladder problems (4), continuous bleeding (4), headache (3), pruritus (3), dryness (1), dizziness (1), eczema (10), amenorrhoea (1), frequent urination (1), increase of uterus myomatosis (1), early menstrual cycle (1) vascular disorders (1)
Loch et al.[41]	1634	Femicur®[b] 2 capsules	3mc	Skin and mucosal symptoms (itching, allergic reaction, vesicles, eczema, urticaria, acne, hair loss) [13]; gastrointestinal tract symptoms (nausea, vomiting, diarrhoea, pain in the stomach, tympanites) [6]; nosebleeding (1), oedema (1), vertigo (1), spotting (1); 18 patients (1.1%) withdrew because of adverse events

a Agnolyt® tincture, MADAUS Germany; 100g of tincture [1:5] contains 9g of VAC.

b Femicur® capsules, Schaper & Brümmer Germany; one capsule contains 1.6–3.0mg dried extract of VAC [6.7–12.5 : 1] corresponding to 20mg drug.

mc = menstrual cycles.

Dittmar et al.,[39] published two drug monitoring studies performed in Germany. 1542 women diagnosed with PMS were treated with Agnolyt® tincture (average dosage of 42 drops daily). The average duration of treatment was 166 days. Thirty-two patients (2.1%) reported the following adverse events: nausea (5), allergy (1), diarrhoea (2), weight gain (1), dizziness (1), heartburn (1), hypermenorrhoea (1), stomach disturbances (3), luteal phase abnormalities (2), acne (3), pruritus (1), redness of skin (2), alopecia (1), palpitations (1), no information (7). Seventeen patients (1.1%) dropped out because of adverse events.

In another postmarketing surveillance study,[40] tolerance of VAC was documented in 551 women experiencing PMS or other gynaecological symptoms. They received 40 drops daily of Agnolyt® tincture. Treatment duration was 1 week to 19 cycles; one-half of the patients were treated for a maximum of four cycles. Twenty-eight patients (5.1%) reported 29 adverse events; the most frequent were nausea (7), stomach or gallbladder problems (4), continuous bleeding (4), headache (3), and pruritus (3). Dryness, dizziness, eczema, amenorrhoea, frequent urination, enlargement of myoma, early menstrual cycle and vascular disorders were each reported once.

The study by Loch et al.[41] involved 1634 women experiencing PMS and was carried out to evaluate the efficacy and tolerance of a new VAC extract (Femicur® capsules, Schaper & Brümmer GmbH, Germany; one capsule containing 1.6–3.0mg dried extract of VAC fruit [6.7–12.5 : 1] corresponding to 20mg drug). Patients received one capsule of the VAC preparation twice daily for three menstrual cycles. Forty-five adverse events were documented in 37 patients (2.3%) and a correlation with VAC treatment was assumed by the investigators in 20 patients (1.2%) reporting 23 adverse events. There were 13 skin disorders (itching, allergic reaction, vesicles, eczema, urticaria, acne, hair loss), 6 gastrointestinal disorders (nausea, vomiting, diarrhoea, pain in the stomach, tympanites) and single cases of nosebleeding, oedema, vertigo and spotting. Treatment was terminated prematurely because of adverse events in 18 patients (1.1%). The tolerance of VAC treatment was described by patients as "very good" (57%), "good" (37%), "moderate" (4%) and "bad" (1%); 19 patients provided no information.

2.3 Data from Surveys

One questionnaire survey on the use of VAC by practitioners of herbal medicine was located.[2] The questionnaire was sent to 280 UK and Ireland members of the National Institute of Medical Herbalists (NIMH) to document the current use of VAC. 155 NIMH members replied. The questionnaire consisted of 15 questions and three of these were about safety, drug interactions and contraindications associated with VAC treatment. 147 practitioners of herbal medicine replied to the question on adverse events: 88 of these (59.9%) reported no adverse events following the use of VAC (predominantly a 1 : 5 tincture); 23 (15.6%) reported minor adverse events (nausea, headache); 20 (13.6%) reported adverse events in an individual patient (nausea, headache, cycle length change, heavier bleeding) and 16 (10.9%) reported adverse events only initially or if the dose was inappropriate.

With regard to drug interactions, the majority of respondents replied that they did not prescribe VAC when the patient was taking orthodox oestrogenic or progestogenic drugs. Of 145 practitioners who replied to the question regarding interactions, 9 (6.2%) reported interactions between VAC and other categories of orthodox medication, but no further details were provided.

In response to the question "are there any conditions that you regard as contraindicated to prescribing Vitex?", 57 of 117 respondents (48.7%) replied "yes". The most frequent conditions were endocrine imbalances (steroid-sensitive cancers [15], pituitary tumour [7], progesterone dominance [8]), breast diseases (6), menstrual cycle abnormalities (menorrhagia [5], dysmenorrhoea [4]), pregnancy (11) and contraceptive pill use (5).

2.4 Data from Case Series/Reports

Four case series[42-45] and four case reports[46-49] were located (table III). In one report,[42] mild premenstrual symptoms were described in a woman with secondary amenorrhoea after treatment with VAC. In another paper,[43] no adverse events were observed in three women with amenorrhoea following treatment with Agnolyt® (40 drops daily for a minimum of 5 weeks). In a paper by Amann,[46] shortened menstruation was observed in a 15-year-

Table III. Adverse events of *Vitex agnus castus* (VAC) reported in case series and case reports

Study	Type of study	No. of patients	Preparation/daily dose	Treatment duration	Adverse events
Probst[44]	Case series	2	Agnolyt®[a] 45 drops	Not specified	Not reported
Albus[48]	Case report	1	Agnolyt®[a] 40 drops	Not specified	Not reported
Hillebrand[49]	Case report	1	Agnolyt®[a] 40 drops	6mo	Not reported
Amann and Kerres[47]	Case report	1	Agnolyt®[a] 120 drops	10d	Not reported
Amann[46]	Case report	1	Agnolyt®[a] 40–80 drops	9mo	Shortened menstruation
Amann[43]	Case series	3	Agnolyt®[a] 40 drops	5wk to 3.5mo	Adverse events not observed
Loch and Kaiser[45]	Case series	20	Agnolyt®[a] 40 drops	Average 6.5mo	Not reported
Blank[42]	Case series	4	VAC 33–40mg	4wk to 3mo	Mild premenstrual symptoms (1)

a Agnolyt® tincture, MADAUS, Germany; 100g of tincture [1 : 5] contains 9g of VAC.

Table IV. Adverse events reported to the spontaneous reporting schemes of the WHO (Sweden), ADRAC (Australia), MHRA (UK) and BfArM (Germany) for *Vitex agnus castus* monopreparations

Adverse event	WHO	ADRAC	MHRA	BfArM
Dermatological symptoms	24	1		28
Gastrointestinal symptoms	19	1		29
General symptoms	13			16
Neurological symptoms	11	3		11
Gynaecological symptoms	9			17
Psychiatric symptoms	8	1		3
Hepatic signs	5			8
Cardiovascular symptoms	2			2
Haematological signs	2			2
Respiratory symptoms	2			5
Visual symptoms	2		1	1
Abortion	1			
Allergic reactions	1			1
Endocrinological signs	1			1
Urinary symptoms				1
Total	**100**	**6**	**1**	**125**

ADRAC = Adverse Drug Reactions Advisory Committee; **BfArM** = Bundesinstitut Für Arzneimittel Und Medizinprodukte; **MHRA** = Medicine and Healthcare Products Regulatory Agency.

old girl after treatment with Agnolyt® tincture (40–80 drops daily for 9 months) for acne. In the remaining papers,[44,45,47-49] there was no mention of the safety or tolerability of VAC treatment.

2.5 Data from Spontaneous Reporting Schemes

2.5.1 WHO Collaborating Centre for International Drug Monitoring

As of July 2003, 75 reports involving VAC monopreparations had been received from the national drug safety bodies of three countries: Germany (72), Austria (1) and Switzerland (2), including a total of 100 adverse events (table IV).

The WHO cautions that the information from this database is not homogenous, at least not with respect to origin or likelihood that the pharmaceutical product caused the adverse events, and that the information does not represent the opinion of the WHO.

The types of reports were postmarketing surveillance/special monitoring (47), spontaneous reports (27) and clinical trial (1). The patients were all women, aged between 14 and 56 years. In the reports, the indications for VAC treatment were excessive menstruation (13), PMS (12), absent menstruation (6), inter-menstrual bleeding (2), menopausal or postmenopausal disorder (3), disorders of menstruation (13), disease of breast (1), uterine leiomyoma (1), abortion (1), contact dermatitis and eczema (1), dysmenorrhoea (2), scanty menstruation (1), pain and other symptoms associated with female organs (2) and not specified (17). The preparations involved in the case reports were the following: Agnolyt®, MADAUS, Germany (44); Strotan®, Stroschein Pharma, Germany (11); Agnucaston®, Bionorica, Germany (18); Agnumens®, Smetana, Austria (1); and Emoton®, Tentan, Switzerland (1).

In each case report except one, VAC was the only suspected drug, although 17 patients were taking concomitant drugs. No possible interactions with other drugs were reported. Seventeen patients recovered, five had not recovered at the time of report and in the remaining 53 patients the outcome was unknown.

In these reports, the causality assessment of the suspected adverse events was probable in 1 case (arteriospasm), possible in 50 cases, unlikely in 9, not assessable in 2, not yet assessed at the time of report in 12 and not specified in 1 case.

In ten cases, an abated reaction was reported following cessation of treatment. No effects were observed in one patient after cessation of treatment with VAC. Rechallenge was performed in four

cases, with a recurrence of symptoms in each patient (abdominal pain, headache, flatulence, depression and fatigue).

There was one case report of abortion following administration of Agnucaston® (Bionorica), but further information regarding the age of the patient, the dose and treatment duration were not provided. The causality assessment was possible.

2.5.2 Bundesinstitut Für Arzneimittel Und Medizinprodukte (BfArM)

BfArM received 89 case reports concerning the following VAC monopreparations: Agnolyt®, MADAUS, Germany (70); Strotan®, Stroschein Pharma, Germany (11); Agno-Sabona, Sabona, Germany (1); Castufemin®, Ardeypharm, Germany (1); and Agnus castus al filmtablet, Aluid Pharma, Germany (6). All cases involved women, and a total of 125 events were reported. The most frequent adverse events were nausea, menstrual disorders, headache, dyspepsia, pruritus and erythematous rash (table IV).

In 65 cases, VAC was the only drug taken by the patient. Although VAC was taken with other drugs in 24 cases, in 22 of these cases it was the only suspected drug. In one case, Stevens-Johnson Syndrome was reported in a 27-year-old patient; there were eight suspected agents (agnus castus extract, dihydroergotaminemesilate, cefadroxil, acetylsalicylsäure, paracetamol, codeinphosphat, ambroxol hydrochloride, erythromycin). In another case, a patient was taking a VAC preparation (agnus castus al filmtablet) with four other drugs (Ketek®, oral contraceptive, Ben-u-ron® and a homeopathic product). She reported facial oedema and pruritus; the VAC preparation and Ketek® were the suspected drugs.

One case of hepatitis associated with bilirubinaemia and increased levels of aspartate aminotransferase and alanine aminotransferase was included in the reports from both the WHO and the BfArM. It involved a 39-year-old woman who had taken 40 drops daily of Agnolyt® for 60 days; the drug was withdrawn and the signs and symptoms were resolved. No further information was given, but the causality was assessed as possible.

2.5.3 Medicine and Healthcare Products Regulatory Agency (MHRA)

Between July 1963 and November 2002, the MHRA had received only one spontaneously reported suspected reaction for a VAC monopreparation (table IV). The report related to a disorder of the eyes (photopsia) in one patient. No causality assessment and no further details were provided.

2.5.4 Adverse Drug Reactions Advisory Committee (ADRAC)

ADRAC provided ten reports of adverse events associated with VAC. Of these, three involved single ingredient products. Six adverse events were reported (table IV). In one of the reports, the name of the product (Herbal Nutrition Vitex 1000) was provided. No further information regarding patient, preparation, dose, treatment duration, concomitant medications, descriptions of causality or outcomes were provided.

2.6 Data from *Vitex agnus castus* Manufacturers

Of the 12 manufacturers of VAC preparations who were contacted, replies were received from six. Three manufacturers did not give additional information about safety data in the form of clinical trials, drug monitoring studies or case reports, but they mentioned the adverse events that are written on the label of their product (occasional itching, urticarial exanthema) and provided information about the possible reciprocal weakening of effects between VAC and dopamine receptor antagonists. Two companies (MADAUS, Germany [Agnolyt® capsules] and Scharper & Brümmer, Germany [Femicur® capsules]) provided details of the adverse events of their preparation that were reported in clinical studies.[18,38] One company (Bionorica, Germany [Agnucaston®]) answered that it was "basically unable to send any case reports to adverse reactions with *Vitex agnus castus*. Those data are confidential/not public and subject to privacy policy". Nevertheless, this company did provide details about the possible undesirable events that have been observed with their product: occasionally pruritic, urticarial exanthema and, in isolated cases, transient psychomotor unrest, confused states and hallucinations.

2.7 Data from Herbalist Organisations

Of the five herbalist organisations that were contacted, a reply was received from three. These organisations had no records of adverse events with VAC monopreparations.

3. Discussion

Natural remedies are often used for the treatment of women's disorders. VAC is probably the most popular herbal remedy for PMS, especially in Germany, where the majority of studies reported in this review have been conducted. Some studies support its efficacy in various female reproductive disorders, but information about the safety of VAC is limited.

The lack of safety data is a recurrent issue with herbal medicine. This is probably because of the misleading notion that herbal medicines are natural and are, therefore, safe. Some plants have been used for hundreds of years and this results in the erroneous belief that they are free from adverse events.[50] There is also evidence that patients inform their physicians about suspected adverse events to herbal medicines in a different manner than to conventional over-the-counter medicines.[51] Thus, the under-reporting of adverse events to herbal medicines is probably substantial.

Our aim was to evaluate all the available safety data of VAC monopreparations, including adverse events, drugs interactions and possible contraindications. Information was obtained from clinical studies, spontaneous reporting schemes, herbal organisations and manufacturers.

Safety data obtained from clinical studies are difficult to interpret because they are usually not designed for evaluating safety. Of five RCTs, one did not give information on adverse events and in one placebo-controlled study, no adverse events were observed. In the other placebo-controlled study, the occurrence of adverse events was comparable between VAC treatment and placebo (4.7% and 4.8%, respectively). In one of the two studies with active controls, the adverse drug reaction rate for VAC was similar to control (VAC = 40%, fluoxetine = 42.8%), whereas in the other study the adverse drug reaction rate for VAC was about 2.5 times higher than for the control treatment (VAC = 19.7%, pyridoxine = 7.7%). The adverse events observed were mild and often noted in only one patient. The other studies located were in most cases old, not well designed, involved a small number of patients and, in some cases, no mention of adverse events was made. Their results largely indicate that there were no serious events and generally the tolerance was described as good. The most frequent adverse events recorded were nausea, acne, allergic reactions, headache and stomach disturbances.

Six postmarketing surveillance studies involving a large patient population (n = 9337) were located. In all these studies, the incidence of adverse events was low and ranged from 1.9% to 5%, which is within the range of nocebo effects.[52,53] Adverse events were mostly mild or moderate and did not seem to impact on withdrawal rates, which ranged from 0.9% to 1.1%. Moreover, some adverse events could have been symptoms of the condition, rather than caused by the treatment itself. The most frequent adverse events reported were nausea, stomach disorders, headache, diarrhoea and acne.

The questionnaire-survey[2] on the use of VAC by practitioners of herbal medicine also implied that the adverse events following use of VAC were generally minor, and in most of the cases the adverse events concerned single patients. The authors of the paper defined the situation as "enigmatic"; some of the contraindications reported by practitioners were the indications that the same practitioners reported for the use of VAC.

The spontaneous reporting schemes of the WHO and BfArM reported 100 and 125 adverse events, respectively, following VAC treatment; some overlap between these data is conceivable. The quality, quantity or frequency of the reports was not sufficient to prove an association between VAC treatment and any specific adverse events; often the patients took other concomitant drugs and information about patient history, dose or treatment duration was usually not provided. Adverse events did not appear to be serious, were generally reported in only one patient and, in some cases, they were the same as the indications for VAC use (reproductive disorders, acne). Several serious or moderately serious events were also noted: abortion, hepatitis, Stevens-Johnson syndrome, glaucoma and peripheral ischaemia. Unfortunately, no detailed information was given. In only one case (peripheral ischaemia), the

relationship to VAC was judged as probable and, in the other cases, there was insufficient information for establishing causality. The most common adverse events were nausea (50%), headache (68%), abdominal pain (17%), acne (15%), pruritus (15%), erythematous rash (17%), weight increase (34%), menstrual disorders (42%) and dyspepsia (19%). Data received from the remaining organisations (ADRAC and MHRA) were not detailed, but serious adverse events were not reported.

No drug interactions emerged from clinical studies or spontaneous reporting schemes. Theoretically, VAC could interact with dopamine-modulating drugs. As reported in the German Commission E monograph,[4] there is experimental evidence of a dopaminergic action of VAC. Therefore, a reciprocal weakening of the effect could occur in cases of concomitant administration of VAC and dopamine receptor antagonists, such as haloperidol or metoclopramide.[54] Moreover, VAC could interfere with other endocrine therapy (hormone replacement therapy, oral contraceptives, sex hormones) because of its action on the pituitary gland. VAC should not be used during pregnancy[14,15,55] because of a lack of toxicity data and it should also be avoided during lactation, although analysis of breast milk revealed no changes in composition.[6]

4. Conclusion

Although further rigorous studies are needed to assess the safety of VAC, the data available to date seem to indicate that VAC is not associated with serious risks to health. The vast majority of adverse events reported were mild and transient, including nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus and erythematous rash. Theoretically, VAC might interfere with oral contraceptives, hormone replacement therapy, sex hormones and dopamine agonists and antagonists.[56] The use of VAC should be avoided during pregnancy and lactation because of a lack of safety data.

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