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ORIGINAL PAPER

Open-label observational study of the homeopathic medicine *Passiflora* Compose for anxiety and sleep disorders

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Background: **Anxiety and sleep disorders (SDS) are frequently treated with psychotropic drugs. Health authorities in France have been advised to improve access to alternative treatments such as homeopathic medicines. Our aim was to describe the socio-demographic characteristics and clinical progression of patients prescribed homeopathic medicine *Passiflora* Compose (PC) for anxiety and/or SDS.**

Material and methods: **This was an open-label, observational study. Randomly selected general practitioners (GPs) known to prescribe homeopathic medicines recruited consecutive patients (≥18-years) prescribed PC. The following data were recorded at inclusion by the GP: socio-demographic data and anxiety severity (Hamilton anxiety rating scale or HAM-A); and by the patients: level of anxiety (STAI Spielberger self-assessment questionnaire) and SDS (Jenkins sleep scale or JSS). Anxiety and SDS were reassessed after 4 weeks of treatment using the same scales.**

Results: **A total of 639 patients (mean age: 46.3 ± 17.5 years; 78.6% female) were recruited by 98 GPs. Anxiety was present in 85.4% (HAM-A) and 93.3% (Spielberger State) at inclusion (mean scores: 17.8 ± 8.91 and 54.59 ± 11.69, respectively) and SDS was present in 74.0% (mean score: 15.24 ± 5.28). A total of 401 (62.7%) patients received PC alone and 167 (26.1%) PC + psychotropics. After 4 weeks, mean anxiety scores decreased by more than 7, 12 and 6 points (HAM-A, Spielberger State and Trait respectively), and SDS score by more than 4 points (JSS).**

Conclusion: **Anxiety and/or SDS improved significantly in patients included on this study. PC could be an alternative to the use of psychotropic drugs for first intention treatment of anxiety and SDS. Further studies are needed to confirm those results.** *Homeopathy* (2015) ■, 1–8.

Keywords: *Passiflora* Compose; Homeopathy; Psychotropic drugs; Anxiety; Sleep disorders; Observational study

Introduction

Mild anxiety and sleep disorders (SDS) are common reasons for consulting a general practitioner (GP). The incidence of SDS in the general population in France has been reported to range from 18.6% to 37.2%,[1–3] with 10% of subjects suffering from chronic insomnia.[3] Insomnia is more common in women than in men and is frequently seen in the elderly.[1,4] Patients who experience insomnia often suffer serious consequences on daytime functioning including daytime sleepiness, impaired concentration, memory problems, decreased efficiency, irritability and difficulties maintaining attention.[1,2] These repercussions can significantly affect quality of life (QoL). The socioeconomic impact of insomnia is also significant, with high rates of healthcare utilisation and absenteeism from work.[4] Anxiety disorders are closely associated with SDS, particularly with sleep onset disorder and problems staying asleep.[1]

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SDS and mild anxiety are often treated with psychotropic drugs such as benzodiazepines. The results of epidemiological studies show that France has the highest annual incidence of psychotropic drug use in Europe (21.4%; Odds ratio = 3.0 [2.4−3.8]), with one person in three taking psychotropic medication at sometime during their lifetime.[5] This high level of use is worrying from an economic perspective and because psychotropic drug use may lead to chronic dependency or withdrawal syndrome.[5] Furthermore, a causal link has been established between psychotropic drug use and many of the daytime consequences commonly attributed to insomnia itself.[1] In June 2006, a parliamentary report on the use of psychotropic drugs recommended that health authorities promote the good use of psychotropics and improve access to alternative treatment strategies such as homeopathic medicines.[5]

Passiflora Compose (PC) (Boiron Laboratories, France) is an association of homeopathic medicines; *Passiflora incarnata* (passionflower) 3DH, *Ignatia amara* (St Ignatius bean) 4CH, *Coffea cruda* (green coffee) 5CH, *Nyckterinia* (midnight candy) 4CH, *Tellurium metallicum* (tellurium) 5CH, *Phosphoricum acidum* (phosphoric acid) 7CH, *Palladium metallicum* (palladium) 5CH, and *Magnesium metallicum* (magnesium) 5CH. Homeopathic medicines associated in PC were traditionally used to treat irritability (palladium), insomnia (passionflower, St Ignatius bean, green coffee, nyckterinia), anxiety (passionflower, St Ignatius bean), depressive syndrome (St Ignatius bean, nyckterinia, phosphoric acid), changing mood (St Ignatius bean, tellurium) or stress-associated somatic symptoms as headache (St Ignatius bean, green coffee, phosphoric acid), gastrointestinal disorders (St Ignatius bean, green coffee), palpitation (green coffee), or muscle pain (St Ignatius bean).[6−10] Moreover, clinical and *in vivo* studies showed that *C. cruda* 30 or 200CH increase sleep duration in human and rat,[11−13] and that various homeopathic dilutions of *I. amara*, including 4CH, reduce anxiety in mice.[14]

PC (oral drops, pillules, tablets) has been prescribed by GP in France for more than forty years. We estimated that approximately four million patients were treated by PC in the last 4 years (internal data). Regarding pharmacovigilance data, no adverse reactions are expected with PC.

The study objectives were i) to describe the socio-demographic and clinical profiles of patients prescribed PC by their GP, the dosages of PC used and the duration of treatment, and ii) to describe the progression of anxiety and SDS over the 4-week study period. For these last analyses, patients were divided into two groups: those given PC alone were compared to patients given PC + psychotropics.

Materials and methods

Study design

This open-label, observational, longitudinal study was carried out between September 2011 and March 2012 among a randomly selected cohort of French GPs who were trained in the prescription of homeopathic medicines. As the study was strictly observational and the patients did not require any supplementary diagnostic or therapeutic investigations ethical approval was not required. Authorisation for the study was granted by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS), the Commission Nationale de l'Informatique et des Libertés (CNIL) and the Conseil National de l'Ordre de Médecins (CNOM). The study was conducted according to the principles of Good Epidemiological Practice edited by ADELF.[15]

Recruitment of GPs

An up-to-date list of 14,102 GPs across France who were known to prescribe homeopathic medicines was provided by Boiron Laboratories to the Contract Research Organization (CRO) and random sampling without replacement was performed to draw up a list of approximately 1800 GPs, with the hypothesis based on previous experience that 8% would agree to take part in the study. The GPs on this list were contacted by telephone and were asked if they prescribe PC in their current practice and would agree to participate, with the aim of establishing a definitive list of 100 active GPs.

Recruitment of patients

Participating GPs were asked to recruit at least five consecutive patients, ≥18-years of age, for whom they had decided to prescribe PC during a medical consultation. GPs received 70 euros per patient to compensate for the additional time required for the study. The only exclusion criteria were: inclusion in another biomedical study during the previous month and an inability to understand French. All patients gave their informed consent to participate in the study. No patient received any remuneration or other incentive to take part.

Data collected

At inclusion: At the inclusion visit, GPs completed an inclusion form recording data on: the socio-demographic characteristics of the patients; the reason(s) for consultation; any treatments taken previously for these symptoms; and details of the prescription of PC or other drugs (formulation, dosage, duration of treatment).

The emotional state of the patient (anxiety severity) was assessed by the GP using the Hamilton anxiety rating scale (HAM-A). This scale grades the severity of 14 symptoms as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = maximum/disabling, giving a total final score ranging from 0 to 56. Anxiety was defined as: normal (final score: 0−8), mild (score: 9−17), moderate (score: 18−24) and severe (score ≥25).

Patients completed a self-assessment questionnaire in private, based on the State-Trait Anxiety Inventory (STAI) Spielberger scale,[16] which assessed their own emotional state. Each Spielberger scale (State or Trait anxiety inventory) consists of 20 questions with scores ranging from: 1 = minimal anxiety to 4 = maximal anxiety. Thus,

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the total score for each scale ranges from 20 to 80. The following total scores were used to classify anxiety in the patients: score: 20−35, very mild; 36−45, mild; 46−55, moderate; 56−65, severe; 66−80, very severe.

Patients also completed a second self-assessment questionnaire designed to assess SDS based on the 4-item Jenkins Sleep Scale (JSS).[17] This concerns "having trouble falling asleep", "waking up several times per night", "having trouble staying asleep" and "waking up after the usual amount of sleep feeling tired and worn out", with a 6-point response scale (1 = never to 6 = every night). Total score for the four items ranges from 4 to 24 (4−12, no or mild SDS; 12−16, moderate SDS; and 16−24, severe SDS). The total score was calculated and a patient was considered to have SDS if the total score was ≥12.

At follow-up: Approximately 4 weeks after inclusion, patients attended a follow-up visit where their GP reassessed their anxiety using the HAM-A scale and completed a follow-up form containing questions on: the clinical progression of the anxiety/SDS; other treatments taken during the study period; and any side-effects linked to PC treatment.

The patients also reassessed their level of anxiety using the STAI self-assessment questionnaire and SDS using the JSS, and answered questions on their compliance.

Statistical analysis

Quantitative variables are described as the mean ± standard deviation (SD), median and range after verification of normal distribution with a Kolmogorov−Smirnov test. Qualitative variables, corresponding to categorical data, are described as number and percent. Independent quantitative variables were compared using the Student's t test or the non-parametric Mann−Whitney or Kruskall−Wallis test if the distribution was not normal. Paired quantitative variables were compared using the paired Student's t test or the non-parametric Wilcoxon signed rank test if the distribution was not normal. Independent qualitative variables were compared using the Chi^2 test and Fisher exact test. Paired qualitative variables were compared using the McNemar Chi^2 test. Performed tests were bilateral with an α risk of 5%. For each scale, the difference of scores between inclusion and end of study (EOS) was compared in a multivariate model adjusted for the score at inclusion (proc mixed).

All statistical analyses were carried out using SAS software, version 9.2.

Results

Participating GPs

A total of 1764 GPs were contacted and 131 returned their agreement forms and took part in the study (participation agreement: 7.4%). These GPs were distributed across the 22 regions of France. GPs recruited a mean of 4.88 ±3.6 patients [range: 0−10] during a period of 6 months. The majority of GPs (53/131; 40.5%) recruited five patients each, but 31 (23.7%) GPs recruited 10 patients each. Twenty-seven (20.6%) GPs did not recruit any patients and six subsequently withdrew from the study resulting in a final participation rate of 74.8% (98/131).

Socio-demographic characteristics of the patients

A total of 639 patients who had taken at least one dose of PC were included in the final analysis. Mean age was 46.3 ± 17.5 years (range: 18−91), 78.6% were female (502/639) and 61.3% were in employment. The socio-demographic characteristics of these patients are summarised in Table 1.

Modalities of prescription of *Passiflora* Compose

GPs prescribed PC for anxiety/irritability in 90.8% of patients and for SDS in 84.8%. SDS and anxiety/irritability were associated in most patients.

Table 1 Socio-demographic and clinical characteristics at inclusion of patients prescribed *Passiflora* Compose (n = 639)

Characteristic	*Number (%)*
Sex	
Male	137 (21.4)
Female	502 (78.6)
Age (years)	
Mean ± SD (range)	46.27 ± 17.48 (18−91)
Socio-professional group*	
Farmer/smallholder	6 (0.9)
Tradesperson, shop, or business owner	22 (3.5)
Management or intellectual professions	72 (11.3)
Intermediate profession	103 (16.2)
Employee	152 (23.9)
Worker	35 (5.5)
Retired	128 (20.1)
Other, no professional activity	118 (18.6)
Reasons for consulting the GP	
Anxiety/irritability	580 (90.8)
Sleep problems	542 (84.8)
Psychotropic drug intolerance	34 (5.3)
Other†	73 (11.4)
Duration of symptoms	
<1 month	163 (25.5)
1−3 months	231 (36.2)
>3 months	245 (38.3)
Psycho-behavioural history in past 3 years	
Depressive episodes	140 (21.9)
Anxiety problems	386 (60.4)
Sleep problems	302 (47.3)
Other‡	15 (2.3)
Psychotropic drug use for these symptoms before the study	
Yes	267 (41.8)
Drugs taken	
Anxiolytics/benzodiazepines	189 (29.8)
Hypnotics	104 (16.4)
Antidepressants	85 (13.4)
Neuroleptics	5 (0.8)
Other§	33 (5.2)

* n = 636.
† Includes: problems with nutrition and metabolism (n = 7), change in general state (n = 4), withdrawal (n = 6), ENT and pulmonary infections (n = 6), cardiovascular symptoms (n = 10), digestive problems (n = 7), rheumatological and trauma symptoms (n = 6), behavioural problems (n = 5), skin disease (n = 1), neurological problem (n = 6), other (n = 15).
‡ Includes: anorexia (n = 2), panic attacks (n = 1), visual hallucinations of unknown aetiology (n = 1), paranoia (n = 1), dietary behavioural problems (n = 1), amnesia and behavioural problems (n = 1), domestic violence (n = 1), unknown (n = 7).
§ Includes: somatic treatment for stress (n = 4), trace elements (n = 4), phytotherapy (n = 16), homeopathy (n = 4), non-medical treatment (n = 2), other psychotropes (n = 3).

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The majority of patients prescribed 5 granules PC 2 times/day. PC treatment was prescribed for 1 month in more than three-quarters of patients (84.9%). The most common reasons for prescribing PC were the absence of known side-effects (75.6%), the absence of any contraindications (73.7%) and previous experience of the efficacy of this medicine (64.5%). In 48% of cases, the patients themselves requested a homeopathic medicine (data not shown).

Four groups of patients were identified depending on the type of medicines taken for anxiety and/or SDS in association with PC: (i) group 1 comprised 401 patients (62.7%) who received PC only; (ii) group 2 consisted of 36 patients (5.6%) who received PC + a non-psychotropic drug with activity on the nervous system (analgesics and/or antihistamines and/or symptomatic treatment for some of the symptoms of anxiety); (iii) group 3 consisted of 167 patients (26.1%) who received PC + a psychotropic drug (at least one anxiolytic and/or benzodiazepine and/or hypnotic and/or antidepressant and/or neuroleptic); and (iv) group 4 comprised 36 patients (5.6%) who received PC + complementary therapies (trace elements and/or phytotherapy and/or vitamins and/or homeopathy and/or food supplements).

Clinical characteristics of the patients at inclusion

At inclusion, anxiety severity was assessed by the GPs using the HAM-A scale and by the patients using the STAI Spielberger self-assessment questionnaire.

Using the HAM-A scale, mild-severe anxiety was diagnosed in 85.4% of patients at inclusion (mean HAM-A score: 17.8 ± 8.91): 38.3% of patients had mild anxiety, 27.2% moderate anxiety and 19.9% severe anxiety (Table 2).

With the Spielberger State anxiety inventory scale, mild-severe anxiety was diagnosed in 93.3% of patients at inclusion (mean State anxiety Spielberger score: 54.59 ± 11.69): 15.1% of patients had mild anxiety, 28.9% moderate anxiety and 49.3% severe or very severe anxiety (Table 2). Mild-severe anxiety was diagnosed in 89.7% of patients at inclusion with the Trait anxiety inventory scale (mean Trait anxiety Spielberger score: 50.63 ± 11.53).

There was a significant correlation between anxiety levels measured using the HAM-A scale and anxiety assessed with the STAI scale ($p < 0.001$).

At inclusion, SDS was assessed by the patients using the Jenkins sleep self-assessment questionnaire. Three-quarters (74.0%) of patients had SDS diagnosed at inclusion (mean score: 15.24 ± 5.28) (Table 2). SDS was assessed as moderate in 23.4% and severe in 50.6% of the study population.

Mean HAM-A and STAI (State and Trait) scores for anxiety and mean JSS score for SDS were significantly higher in the group given PC + psychotropics (20.84 ± 9.54, 58.05 ± 11.4, 54.86 ± 10.69 and 16.20 ± 5.10, respectively) than in patients given PC only (16.75 ± 8.61, 53.52 ± 11.65, 48.92 ± 11.54 and 14.85 ± 5.36, respectively) ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p = 0.006$). The proportion of patients with severe anxiety and SDS was significantly higher in the group given PC + psychotropics than in those given PC only ($p < 0.001$; $p = 0.004$, $p < 0.001$ and $p < 0.001$) (Table 3).

Two-thirds of patients (60.4%) had a history of anxiety during the previous 3 years and 47.3% had a history of SDS (Table 1). Two-thirds of patients (61.7%) prescribed PC had recent anxiety and/or SDS (≤3 months prior to the study) (Table 1). The proportion of patients with a

Table 2 Evolution of anxiety and sleep disorders during the study

Clinical state	*At inclusion (%)*	*At end of study (%)*	p
Anxiety (Hamilton scale*)	N = 639	N = 614	
Mean score (range)	17.8 ± 8.91 (1.0–56.0)	10.32 ± 7.73 (0.0–49.0)	<0.001
No anxiety	14.6%	49.4%	
Mild	38.3%	35.3%	
Moderate	27.2%	9.6%	
Severe	19.9%	5.7%	
Anxiety state (Spielberger scale†)	N = 608	N = 590	
Mean score (range)	54.59 ± 11.69 (21.0–80.0)	42.47 ± 11.88 (20.0–80.0)	<0.001
No anxiety	6.7%	29.8%	
Mild	15.1%	36.4%	
Moderate	28.9%	19.5%	
Severe and very severe	49.3%	14.3%	
Anxiety trait (Spielberger scale†)	N = 614	N = 574	
Mean score (range)	50.63 ± 11.53 (22.11–80.0)	43.76 ± 10.42 (20.0–76.84)	<0.001
No anxiety	10.3%	22.3%	
Mild	25.6%	36.2%	
Moderate	26.7%	27.9%	
Severe and very severe	37.4%	13.6%	
Sleep disorder (Jenkins scale†)	N = 581	N = 579	
Mean score (range)	15.24 ± 5.28 (4.0–24.0)	10.76 ± 4.67 (4.0–24.0)	<0.001
No sleep disorder	26%	60.4%	
Moderate	23.4%	22.3%	
Severe	50.6%	17.3%	

p values determined with the Wilcoxon test.
* Assessed by the GP.
† Assessed by the patient.

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Table 3 Anxiety and sleep problems at inclusion in patients given *Passiflora* Compose only compared to those given *Passiflora* + psychotropic drugs

Clinical state	Passiflora *only*	Passiflora *+ psychotropics*	p
Anxiety (Hamilton scale*)	N = 401	N = 167	
Mean score (range)	16.75 ± 8.61 (1.0–45.0)	20.84 ± 9.54 (2.0–56.0)	<0.001
No anxiety	18.7%	6%	
Mild	38.2%	34.1%	
Moderate	25.9%	31.1%	
Severe	17.2%	28.7%	<0.001
Anxiety state (Spielberger scale†)	N = 382	N = 157	
Mean score (range)	53.52 ± 11.65 (22.0–80.0)	58.05 ± 11.4 (21.0–80.0)	<0.001
No anxiety	7.3%	3.8%	
Mild	16.5%	9.6%	
Moderate	30.4%	27.4%	
Severe and very severe	45.8%	59.2%	0.004
Anxiety trait (Spielberger scale†)	N = 385	N = 160	
Mean score (range)	48.92 ± 11.54 (24.0–80.0)	54.86 ± 10.69 (22.11–80.0)	<0.001
No anxiety	12.2%	4.4%	
Mild	30.1%	16.3%	
Moderate	26.5%	28.1%	
Severe and very severe	31.2%	51.3%	<0.001
Sleep disorder (Jenkins scale†)	N = 366	N = 151	
Mean score (range)	14.85 ± 5.36 (4.0–24.0)	16.20 ± 5.10 (4.0–24.0)	0.006
No sleep disorder	29.8%	17.9%	
Moderate	24.0%	21.9%	
Severe	46.2%	60.3%	<0.001

p values determined with the Wilcoxon test.
* Assessed by the GP.
† Assessed by the patient.

history of anxiety, SDS and depression, and with anxiety and/or SDS of longer duration (>3 months) was significantly higher in the group prescribed PC + psychotropics than in those taking PC only (59.3% of patients with anxiety >3 months for PC + psychotropics vs. 31.4% for PC only; $p < 0.001$) (data not shown).

Clinical evolution of the patients

Anxiety: Six hundred and fourteen patients were included in the final analysis of Hamilton anxiety since 25 patients did not attend for follow-up. Overall, mean HAM-A score for anxiety decreased from 17.8 ± 8.91 to 10.32 ± 7.73 at EOS (Table 2), a statistically significant ($p < 0.001$) decrease of −7.48 points (42.1%). Anxiety improved in 62.4% of patients (defined as a change in class), was stable in 35% and became worse in 2.6% of patients.

Mean Spielberger State anxiety inventory score decreased from 54.59 ± 11.69 to 42.47 ± 11.88 at EOS (Table 2), a statistically significant ($p < 0.001$) decrease of −12.12 points (22.3%). Anxiety improved in 70.4% of patients, stabilised in 22.3% and became worse in 7.3%.

Mean Spielberger Trait anxiety inventory score decreased from 50.63 ± 11.53 to 43.76 ± 10.42 at EOS (Table 2), a statistically significant ($p < 0.001$) decrease of −6.87 points (13.6%). Anxiety improved in 50.7% of patients, stabilised in 39.8% and became worse in 9.5%.

In the multivariate model, there was a significant difference in the progression of anxiety scores between patients given PC alone (decrease of −7.5, −12.6 and −6.85 points for HAM-A, Spielberger State and Trait anxiety, respectively) compared to those given PC + psychotropics (decrease of −7.1, −10.35 and 5.76 points, respectively) ($p = 0.0002$, $p < 0.0001$ and $p < 0.0001$) (Figure 1).

Sleep disorders: Mean score for SDS decreased from 15.24 ± 5.28 to 10.76 ± 4.67 at EOS (Table 3), a statistically significant ($p < 0.001$) decrease of −4.48 points (29.4%). Overall, SDS improved in 53.9% of patients, remained stable in 40.1% and deteriorated in 6%.

In the multivariate model, there was a significant difference in the evolution of SDS score between patients given PC alone (JSS decrease of −4.9 points) compared to those given PC + psychotropics (decrease of −3.4 points) ($p < 0.0001$) (Figure 1).

Compliance

Only half (n = 314; 53%) of the patients respected the GP's prescription exactly. However, of the patients (n = 279) who did not strictly comply with the PC prescription, most (243; 87.1%) forgot to take a dose only two or three times during the 4-week study period. Thus, taking these patients into consideration, compliance was good for 94% of patients (557/592 patients for whom data were available). Of the remaining 6%, 5.2% forgot to take their treatment for more than 1 week during the study and 0.5% never took their treatment.

Adverse events (AE)

PC was well-tolerated. Only five patients (0.8%) suffered an AE which was considered by the GP to be linked to PC treatment (nightmares n = 1, excitation insomnia n = 1, irritability n = 1, lethargy n = 1, hot in the head in the context of psychosis n = 1).

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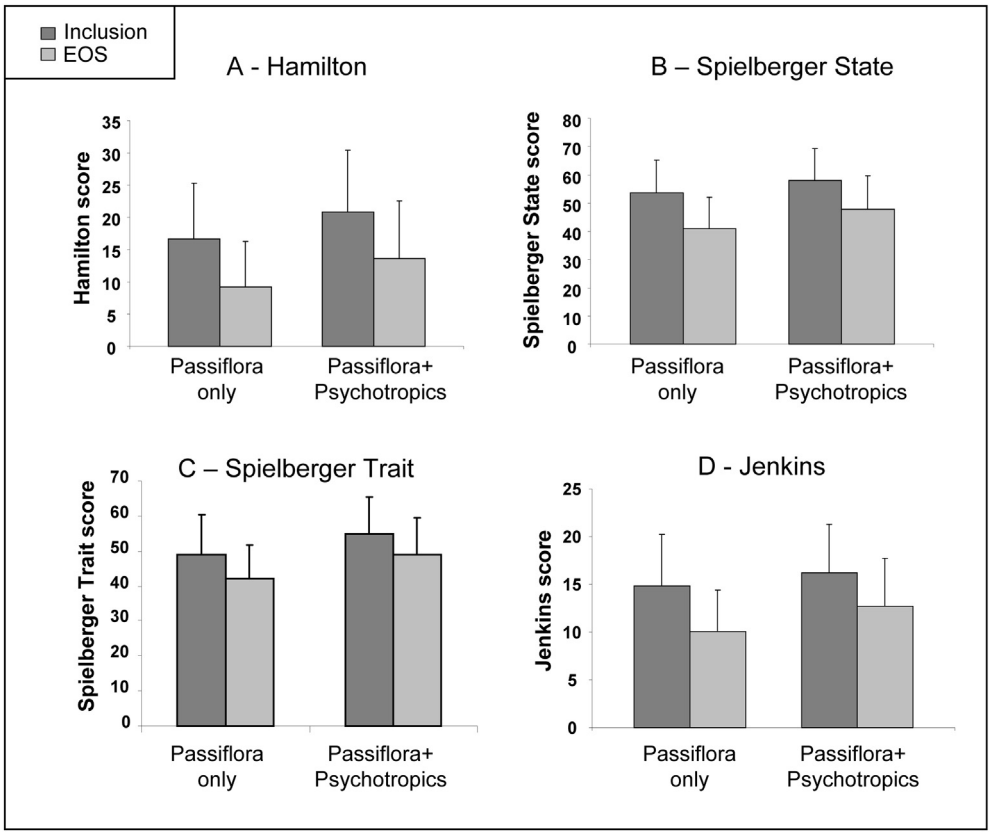

Figure 1 Evolution of anxiety and sleep disorders according to the treatments prescribed in the study. This figure illustrates score changes in Hamilton Anxiety Scale (A), Spielberger State anxiety inventory (B), Spielberger Trait anxiety inventory (C) and Jenkins sleep disorders (D) at inclusion and at the end of study (EOS) for patients given *Passiflora* Compose only and patients given *Passiflora* Compose + Psychotropics.

Change in psychotropic drug use during the study

In the month preceding inclusion, 267 patients (41.8%) had already received treatment for anxiety and/or SDS: 29.8% of patient had received anxiolytics/benzodiazepines, 16.4% hypnotics, 13.4% antidepressants, 0.8% neuroleptics and 4% alternative therapies (phytotherapy 2.5%, homeopathy 0.6%, trace elements 0.6%, non-medicinal therapy 0.3%) (Table 1). The exact date when these treatments were started for each patient is unknown. One-third of these patients continued treatment with anxiolytics, benzodiazepines and/or hypnotics and one-half with antidepressants during the study. However, 50% of the patients taking anxiolytics/benzodiazepines and 40% taking antidepressants had stopped these treatments 16−30 days before inclusion in the study.

During the study, PC was associated with anxiolytics/benzodiazepines in 10% of patients, with hypnotics in 6.6%, with anti-depressants in 6.4%, with phytotherapy in 0.6% and with another homeopathic medicine in 1.2%.

At EOS, 9.9% of patients were prescribed anxiolytics/benzodiazepines, 4.1% hypnotics, 5.9% antidepressants and 76.5% were given a repeat prescription of PC. Thus, patients who were prescribed PC in this study did not use new psychotropics during the study or at EOS. The change in psychotropic drug use before, during and after the study is summarised in Figure 2.

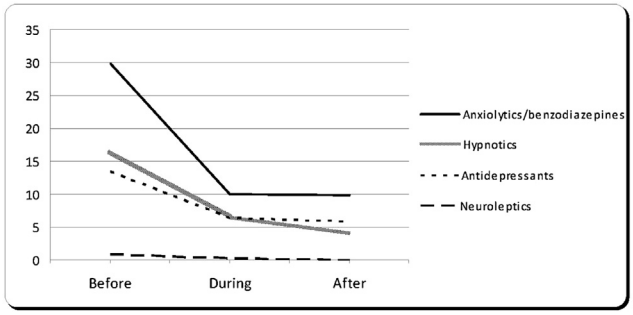

Figure 2 Percentage of patients receiving treatment with each class of psychotropic drug in the month before the study, during the study and at the end of the study (EOS).

Discussion

Previous studies have been conducted to evaluate the efficacy of homeopathic medicines for reducing anxiety. Systematic reviews concluded that results do not preclude the possibility of some benefit for homeopathic medicines but no robust conclusion could be given.[18,19] Authors suggest further investigation with pragmatic design and qualitative studies.

This open-label, observational, longitudinal study carried out between September 2011 and March 2012 shows that the majority of patients prescribed PC by GPs in

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France were female (78.6%) and middle-aged (mean age: 46.3 ± 17.5 years). These results are coherent with observations from previous epidemiological studies on the use of CAM.[20–22] The majority of our patients had a history of depression, anxiety and sleep disturbances over the 3 years prior to the study and nearly half (41.8%) had received psychotropic drugs for these symptoms before taking part. The main reasons for PC prescription in this study were anxiety and SDS, usually occurring concurrently in the same patient. In 62.7% of cases, PC was prescribed alone and in 26.1% it was prescribed in association with a psychotropic drug.

PC alone was prescribed mainly to patients with mild to moderate anxiety according to the HAM-A scale, although nearly 1/5 patients (17.2%) prescribed PC alone had severe anxiety. Nearly half of the patients (46.2%) prescribed PC alone also had severe insomnia according to JSS. Thus the GPs integrated PC, which contains several components including *P. incarnata, I. amara, C. cruda*, and *Nyckterinia* reported to be helpful in SDS,[6,7] into their prescription for severe insomnia. However, the proportion of patients with severe SDS was significantly higher in the group of patients prescribed PC + psychotropics compared to those given PC alone (60.3% vs. 46.2%, respectively) as was the percentage of patients with severe anxiety (28.7% (HAM-A), 59.2% (STAI) vs. 17.2% and 45.8%, respectively). Thus, GPs prescribed psychotropics in addition to PC to patients with more severe symptoms.

In agreement with PC traditional use, anxiety and SDS both improved significantly according to the different scales in patients who were prescribed PC (mean anxiety score (HAM-A) decreased from 17.8 ± 8.91 at inclusion to 10.32 ± 7.73 at EOS, mean anxiety score (Spielberger State and Trait anxiety inventory) decreased from 54.59 ± 11.69 to 42.47 ± 11.88 and from 50.63 ± 11.53 to 43.76 ± 10.42, respectively, and mean SDS score (JSS) decreased from 15.24 ± 5.28 to 10.76 ± 4.67). Furthermore, there was a statistically more favourable improvement in anxiety (both HAM-A and STAI scales) and SDS scores in patients given PC alone compared to those taking PC + psychotropics ($p = 0.002$; $p < 0.0001$; $p < 0.0001$; $p < 0.0001$). This may be due to the fact that patients given PC + psychotropics had more severe anxiety and SDS at inclusion than those given PC only. A randomised controlled clinical trial with anxiety and SDS severity equilibrated groups is required to determine whether patients with severe anxiety given PC alone can be improved to the same extent as patients given psychotropic drugs.

The DGS (Direction Générale de la Santé), High Authority of Health (HAS) and National Agency for the Safety of Medicines and Products of Health (ANSM) in France have made a commitment through an action plan aimed at promoting the reasonable consumption and responsible use of benzodiazepines. Benzodiazepines are associated with a number of side-effects including impaired cognitive performance, particularly short-term memory, and antidepressants have been associated with increased suicidal tendencies.[5] Thus, the benefit/risk ratio of prescribing these medicines should be thoroughly assessed before prescription and alternative therapies prescribed wherever possible. Homeopathic medicines such as PC could be a feasible alternative treatment option in some patients if we consider: (i) the evolution of anxiety and SDS in our group of patients given PC alone; (ii) that patients did not use new psychotropic drugs during the study; (iii) that three-quarters of patients (76.5%) were given a repeat prescription of PC at EOS; and (iv) the good tolerance of PC during the study (only 0.8% AEs). Those preliminary results need to be considered for setting up further more rigorous study on PC.

This study has several strengths. First, the population size was large (n = 639) and the GPs were distributed across all 22 regions of France. Second, the clinical evolution of patients taking PC alone (n = 401) was compared to that of patients taking PC + psychotropic drugs (n = 167) using recognised and validated measurement scales for anxiety and SDS (HAM-A and JSS scales).

A major limitation to the study is the absence of a placebo control group. A placebo effect cannot be excluded and a randomised double-blind, placebo-controlled clinical trial is necessary to confirm the efficacy of PC at decreasing anxiety and SDS. Furthermore, the study was open-label and both the patients and GPs were aware of the medications prescribed, thus opening the results to potential bias in the interpretation of the results. In this study, we observed results on anxiety and SDS after one month of treatment. This period could be considered as relatively short, especially if we take into account that one third of patients had anxiety for more than 3 months at inclusion visit.

Conclusion

This observational study shows that anxiety and SDS improved significantly in the majority of patients who received PC and that this treatment was well-tolerated. PC is a potential alternative therapy to psychotropic drugs for first intention treatment of anxiety and SDS. Further well designed, double-blind, placebo-controlled clinical trials are necessary to confirm these results. The use of homeopathic medicines like PC is in accordance with HAS recommendations on limiting the use of benzodiazepines with their associated side-effects.

Conflicts of interest statement

All the authors are employees of Boiron Laboratories. This study was funded by Boiron Laboratories.

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