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ORIGINAL ARTICLE

Effect of *Gelsemium* 5CH and 15CH on anticipatory anxiety: a phase III, single-centre, randomized, placebo-controlled study

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ABSTRACT

Therapeutics to treat or prevent anxiety are numerous but many people choose to try non-conventional medicine such as homeopathy. This study aimed at evaluating the effectiveness of *Gelsemium* 5CH and 15CH on provoked anxiety in healthy volunteers, in comparison with placebo. This was a double-blind, single-centre, randomized, placebo-controlled study. Eligible healthy men or women aged from 18 to 40 years without a history of psychiatric disorders were randomly allocated to receive *Gelsemium* 5 or 15CH or placebo. Anxiety was proved by performance of the Stroop colour word test (SCWT). The primary end-point was anxiety assessed by the State measure of the State-Trait Anxiety Inventory (STAI-S) as the absolute value and difference with baseline, according to the treatment received. We included 180 healthy volunteers. The distribution into each treatment group was homogenous. There was no statistical difference between groups for the values of STAI-S at baseline, just before the SCWT and the difference between these times (1.8 [0.20 to 3.4], 1.0 [−0.6 to 2.6] and 1.4 [−0.3 to 3.0] for *Gelsemium* 15CH, 5CH and placebo respectively). Likewise, no statistical difference was observed between groups in anxiety as measured by a Visual Analogue Scale and the Competitive State Anxiety Inventory. Mean arterial pressure and heart rate significantly increased ($P < 0.001$) but no interaction between time prior to provoked anxiety and treatment was shown ($P = 0.59$ and $P = 0.46$, respectively). *Gelsemium* 5CH and 15CH do not prevent anticipatory anxiety in the conditions used in this study.

INTRODUCTION

Anxiety is described by two components [1,2]: trait and state anxiety. Trait anxiety is an acquired behavioural disposition, which predisposes a person to perceive a wide variety of objectively innocuous circumstances as threatening. In response, the reactions of the individual are out of proportion to the real danger. State anxiety is characterized by a subjective unpleasant feeling of fear or worry in particular situations. This feeling can involve psychological tension and activation of the autonomic nervous system. State anxiety is particularly frequent prior to competitions and exams for example. In the latter, state anxiety is maximal before the test and disappears during the test and is thus called anticipatory anxiety.

Therapeutics to treat or prevent anxiety are numerous including drugs, relaxation therapies, sessions of psychoanalysis, etc. The reference drug treatment for state anxiety is with benzodiazepines. These are effective but have numerous adverse side effects. Betablockers are sometimes used, but these affect cardiovascular performance. Serotonin reuptake inhibitors have been shown to be effective in the treatment of anxiety, but their action appears only 2–3 weeks after the introduction of the treatment. Antihistaminic drugs may also represent an interesting treatment but subjects may experience fewer efficacies than with benzodiazepines. These reasons explain why many people choose to try alternative medicines, such as homeopathy, to decrease anticipatory anxiety. Many people consider homeopathy more suitable for them, especially when they are not suffering of a particular anxiety disorder.

Among all the homeopathic agents, our attention was drawn to *Gelsemium*, which is obtained from the dried roots of Carolina Jasmine. Its pathogenic action leads to muscular weakness with a feeling of fatigue, associated with trembling and neurovegetative symptoms. It can be toxic at high doses, as it can cause sedation associated with paralysis of the respiratory muscles. Thus, *Gelsemium* is prescribed at ultra low doses, according to the principles of homeopathy, for its action against anxiety, its effects on curarization and sedation. Some studies have shown that, in mice, *Gelsemium* could prevent induced stress [3] or will have anxiolytic-like effects [4]. Furthermore, recent studies [5,6] explored the pharmacological effects of *Gelsemium* on allopregnanolone that plays a key role in the modulation of neurological and psychopathologic symptoms such as anxiety.

In current homeopathic practice, *Gelsemium* is widely prescribed to prevent provoked-stress, notably prior to exams, in young adults who prefer not to resort to the traditional anxiolytics. However, to date no clinical studies have shown the effectiveness of this homeopathic treatment for provoked anxiety.

Various methods are used to provoke anxiety to study the effectiveness of anxiolytic drugs and the effects of stress on the body. These include projections of facial expressions to revive some painful or traumatic memory [7], anticipation of mild electric shocks [8] or surprise painful stimulation [9]. A method to provoke anxiety that is not constraining and not traumatic for the volunteers, and which has been validated and used by several other research teams [10–15], is the use of the Stroop colour word test (SCWT). This test has been shown to provoke physiological stress with an increase in plasma and urinary epinephrine [16]. It is easy to use reproducible and conforms to ethical principles. The difficulty of the test depends on the conflict between a voluntary process (focusing on the colour of the ink – to follow the test's consign) and an automatic process (such as reading). The test has been modified and validated by Leite et al. [15] for use as a model of experimentally induced anxiety using unpleasant noises when errors occur and with continuous video recording.

The objective of this present study was to evaluate the effectiveness of *Gelsemium* at two dilutions, 5CH and 15CH, on provoked anxiety in healthy volunteers, in comparison with placebo. Anticipatory anxiety was quantified using the State part of the 'State-Trait Anxiety Inventory' (STAI) as the main criterion. An anxiety visual analogical scale (VAS) was used as a secondary outcome criterion.

MATERIALS AND METHODS

Study participants

Healthy male or female volunteers aged between 18 and 40 years were recruited from the Grenoble Clinical Research Centre healthy volunteer register or by means of advertisement in the local press, between 8 June 2009 and the 15 April 2010.

Exclusion criteria were a history of psychiatric disorders including psychosis; a history of psychiatric hospitalization; use of psychiatric treatment (antidepressants, antipsychotics or mood stabilizers) in the previous year; use, even a single dose, of psychotropics belonging to or related to the class of benzodiazepines or of any sedatives (phytotherapy, homeopathy, sedatives containing bromine or trace minerals) or antihistamines or use of propranolol in the month preceding inclusion in our study; declared addiction, any disability that could lead to difficulty in performing the SCWT (blindness, colour blindness, poor vision, dementia, speech disorders); pregnancy, parturiency or breastfeeding and allergy to any constituent of the globules (lactose and saccharine).

Objective and end-points

The main objective was to evaluate the efficacy of *Gelsemium* 5CH and 15CH on provoked anticipatory anxiety.

The primary outcome was the anxiety level as assessed by the 'State' part of the State-Trait Anxiety Inventory (STAI-S), both as an absolute value and as the change from baseline, according to the treatment received (*Gelsemium* 5CH, 15CH or placebo). The 'State-Trait Anxiety Inventory (STAI)' [2] was developed by

Spielberger in 1966 and is composed of two parts to evaluate the state and the trait components of anxiety. A French version of this measure was developed and validated [17]. The STAI consists of 40 questions (20 in each part), takes about 15–20 min and is widely used in clinical practice and clinical research.

Secondary objectives were to assess efficacy of *Gelsemium* on provoked anticipatory anxiety using a VAS and the Evaluation de l'Etat d'Anxiété à la Compétition (EEAC) scale [18], a French version of the Competitive State Anxiety Inventory-2 [19]. The latter is an auto-evaluation scale composed of three subscores: self-confidence, cognitive anxiety and somatic anxiety, usually administered and validated to quantify the level of stress of a competitor before a sports competition. We also measured Trait part of State-Trait Anxiety Inventory (STAI-T) and performed continuous recording of arterial pressure, heart rate and respiratory rate.

Study design

This was a single-centre, parallel, double-blind, randomized, placebo-controlled study with three groups: a placebo group, one group receiving *Gelsemium* 5CH and the other receiving *Gelsemium* 15CH.

Volunteers had to attend the Grenoble Clinical Research Centre three times: first for a pre-inclusion visit (V0) 14 days before the study visit (D-14 ± 7), then an inclusion visit (V1, D-7 ± 3) and the study visit (V2, D0).

During the pre-inclusion visit, eligibility was checked and volunteers were informed about the study; a medical examination was performed and clinical parameters measured: arterial blood pressure, heart rate and respiratory rate (Infinity Gamma XL; Dräger Medical Systems Inc, Danvers, MA, USA).

After a few days for reflexion, the volunteer attended the inclusion visit (V1), when inclusion and exclusion criteria were checked and the volunteer was requested to sign the informed consent form. The clinical parameters were again measured. Anxiety level was assessed using three different scales: STAI-S and T, EEAC and VAS. The volunteers were also asked to fill in a questionnaire about their opinion of homeopathy. Electronic randomization through a website was immediately performed and the experimental product was dispensed.

During the morning of the fifth day before the main study visit (V2, D-5), volunteers had to complete the STAI-S, STAI-T, EEAC forms and VAS scale, whilst at home in calm surroundings. These measures were used as the baseline data. We asked volunteers to delay this self-assessment to D-4 or D-3 in case of unexpected stress on D-5. In the event of missing 'home' data, the data collected at V1 were used.

For the study visit V2, the volunteer was welcomed on arrival in the morning at the Clinical Research Centre day care facility and installed on a bed in a single room by a nurse. The procedure of the visit was exactly the same for all participants. A physician checked inclusion and exclusion criteria, adverse events (AE), concomitant treatments, observance of the *Gelsemium* medicine, verified that the forms and scale had been correctly completed at home and explained the course of the visit. The computer for the SCWT and microphone were placed in front of the volunteer and headphones were put on. Arterial blood pressure, heart rate and respiratory rate were measured again, and then the device to continuously monitor arterial blood pressure and heart rate (Nexfin monitor; Bmeye B.V., Amsterdam, the Netherlands) fitted and started. The nurse asked the volunteer to fill in the anxiety VAS, STAI-S and EEAC scales in this order. Then, the instructions for the SCWT were read to the volunteer. This procedure was standardized to be the same for all participants. The words of the SCWT appeared on the screen of the computer and simultaneously the volunteer heard a neutral voice saying a random colour name (to cause confusion). This anxiety test was divided into two parts of equal difficulty and duration (100 words each time). After the first part of the SCWT, the participants again filled in the anxiety VAS, STAI-S and EEAC scales. Then, the second part of the SCWT was performed. When finished, the device to continuously measure arterial blood pressure and heart rate was removed. For a last time, the participants completed the anxiety VAS, STAI-S and EEAC scales and a questionnaire about their opinion of homeopathy after having taken part in the study. Throughout this visit, a camera was placed in front of the volunteer and recorded the scene. The results of the SCWT were not given to volunteer, and they were asked to not to discuss the test with other potential participants they might know.

Treatment

The treatment was composed of placebo, *Gelsemium* 5CH or *Gelsemium* 15CH. All volunteers had a consultation with a pharmacist at V1. During the study, they took five doses of globules: a morning and an evening dose on the 2 days preceding V2 and the last dose on the morning of V2. To increase observance, the pharmacist phoned all volunteers on D-4 or D-3 before their V2. The pharmacist also checked that no stressful event occurred and that volunteer had filled in the questionnaires at home.

Treatments and standardized explanations were given by the pharmacist who was blinded to the randomization.

Adherence to treatment was checked during the V2 by inspecting the boxes of 'treatment' initially containing six doses and questioning the volunteer about taking the treatment.

Randomization and blinding

NQuery Advisor® (Statistical Solutions, Saugus, MA, USA) was used to create a randomization list allowing the repartition of volunteers into three groups. Block size was 6. Stratification was performed at inclusion on the basis of gender and level of STAI-T with cut-offs of 35.55 for men and 36.15 for women (mean scores observed in a population of 19- to 39-year-olds).

To ensure double blinding, treatments were sampled and labelled by the manufacturer (Boiron) according to a randomization list prepared by an independent statistician. All treatments had the same appearance, taste and texture; and during the study, no one had access to the randomization list. The hospital's pharmacy had a copy of the list in case of need to break the blinding in an emergency. All the envelopes concerning randomization remained sealed until the end of the statistical analysis.

Sample size and statistical analysis

Our objective was to observe a 10% decrease in the average STAI-S score (41 ± 8.9 to 36.9) similar to that found by Teixeira-Silva using Diazepam [13] in the group treated with *Gelsemium*, with a risk α of 0.05% and a power of 80%. This required enrolment of 59 persons per group. To allow for potential losses, 60 per group were planned, requiring a total of 180 volunteers. All analyses were performed in intention to treat.

Quantitative data were described by mean and 95% confidence interval (CI). Qualitative data were described by size, percentage and 95% CI. For the primary end-point, if the statistical conditions were met, an ANOVA test was performed. If homogeneity of variances and/or the normality of the parameter were not met, the non-parametric test Kruskal–Wallis test would be implemented. We then applied the Mann–Whitney test to compare groups pairwise after Bonferroni correction.

RESULTS

Study population

Two hundred and thirty-seven volunteers were assessed for eligibility, and 180 healthy volunteers were included between June 2009 and April 2010. The distribution into each group and the reasons for non-enrolment are shown in *Figure 1*. The characteristics of the population at inclusion are described in *Table I* and the volunteers' opinions about homeopathy before taking the treatment in *Table II*.

Because of the stratification, the distribution of volunteers into each treatment group was homogenous.

Primary end-point

There was no statistical difference between the groups for the values of STAI-S at baseline, before the SCWT and the difference between these times (*Table III*). *Figure 2a* shows the evolution of the STAI-S score during the visit V2.

Secondary end-points

No statistical difference was observed between the groups for the evaluation of the anxiety by VAS (*Figure 2b* and *Table III*). The results for the three subscores of EEAC are given in *Table III*. When patients were divided in two groups depending on their baseline STAI-T (above and below median), subgroup analysis showed no difference between groups on STAI-S, VAS and EEAC scores (data not shown).The mean arterial pressure significantly increased during the study ($P < 0.001$; *Figure 2c*) but no interaction between time and treatment was shown ($P = 0.59$). Similarly, the heart rate significantly increased between V1 and the end of the SCWT ($P < 0.001$; *Figure 2d*), but no interaction was found ($P = 0.46$). Respiration rates (cycles per minutes [cpm]) were not statistically different between the three groups for the two study visits (16.1 ± 3.0, 16.6 ± 2.5 and 16.0 ± 2.3 at V1 for *Gelsemium* 15CH, *Gelsemium* 5CH and placebo respectively, $P = 0.450$; 16.7 ± 2.3, 17.3 ± 2.5 and 16.8 ± 2.1 at V2 for *Gelsemium* 15CH, *Gelsemium* 5CH and placebo respectively, $P = 0.282$).

Subsequently, we performed a per protocol analysis, i.e. including only volunteers who took the complete treatment and for whom the primary end-point was available: 56 persons in the *Gelsemium* 15CH group, 58 in the *Gelsemium* 5CH group and 54 in the group who received placebo. The conclusions were the same (data not shown).

Volunteers' opinions on homeopathic treatment

No change in opinion on homeopathy was found when we compared the replies of volunteers to the question 'Do you think that homeopathic therapy is generally effective?' at visits V1 and V2: 23.46% of the volunteers

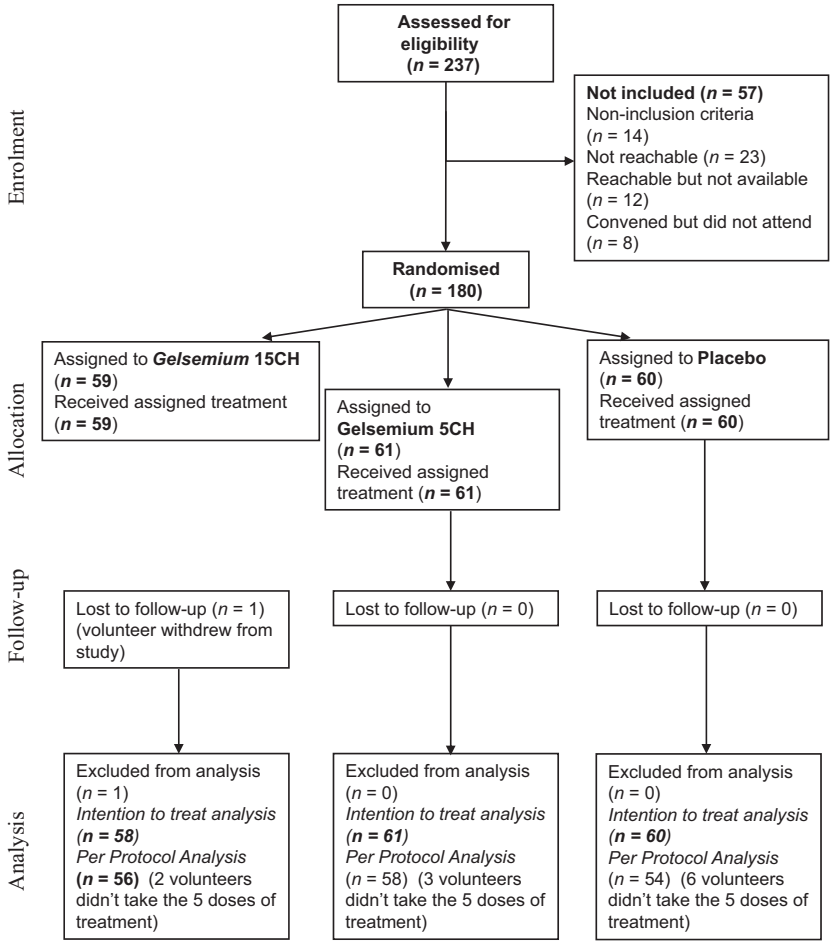

Figure 1 Flow chart of the study.

always replied 'No', 34.64% always replied 'Yes' and 41.90% had no opinion. We compared the evolution of the STAI-S during the study according to the opinion about homeopathy. There was no difference between groups ('No', 'Yes' and 'No opinion') at any point in the study ($P = 0.99$).

Adverse events

During the study, 36 AE were reported by 35 volunteers. No relation with the experimental product was found. No Serious AE occurred. The distribution of AE between the three groups was similar (16.9% for *Gelsemium* 15CH, 21.3% for *Gelsemium* 5CH and 20.0% for placebo; $P = 0.83$).

DISCUSSION

The homeopathic treatment administered in our study to healthy volunteers had no effect on anticipated anxiety, whatever the judgement criteria used.

Anxiety is among the most common reasons for individuals to seek treatment with complementary therapies such as homeopathy [20]. Numerous investigations have been performed to evaluate the effect of homeopathic treatment on anxiety. In 2006, Pilkington et al. [21] published a systematic review on the subject of anxiety and anxiety disorders. They found eight randomized clinical trials, four uncontrolled studies, one pragmatic outcome study, numerous single-case reports, surveys and audit/patient outcome studies. For test anxiety, two studies have been reported: one for which the original article was unavailable [22]. Nevertheless, it was a controlled trial comparing *Argentum Nitricum* 12DH to placebo in 40 people. The anxiety was evaluated by the Test Anxiety Scale and was significantly reduced in the group that received homeopathic treatment. In the second study, a repeat of the first [23], 70 test anxious students were included and randomized to one of the three groups: traditional homeopathy preparation of *Argentum Nitricum* 12DH, radionic prep-

Table I Study population.

	Gelsemium 15CH (n = 59)	*Gelsemium* 5CH (n = 61)	Placebo (n = 60)
Gender male, *n* (%)	24 (40.7)	25 (41)	25 (41.7)
STAI-T score (18–80)[a]			
Low stratum, *n* (%)	35 (59.3)	35 (57.4)	35 (58.3)
High stratum, *n* (%)	24 (40.7)	26 (42.6)	25 (41.7)
Age (18–40 years)			
Mean (SD)	23.6 (3.8)	23.3 (4.1)	23.8 (4.1)
Median (25°; 75°)	23 (22; 24)	22 (21; 24)	23 (21; 25)
Body mass index			
Mean (SD)	21.6 (3.5)	21.8 (2.7)	21.6 (3.3)
Median (25°; 75°)	21.1 (19.5; 23)	21.4 (19.7; 23)	21.1 (19.3; 23)
Systolic arterial pressure, mmHg			
Mean (SD)	121.7 (11.1)	119.9 (9)	118.1 (9.3)
Median (25°; 75°)	121 (113; 129)	119 (114; 126)	119 (110.5; 125)
Diastolic arterial pressure, mmHg			
Mean (SD)	71.4 (9.1)	71.5 (7.7)	72.4 (8.1)
Median (25°; 75°)	71 (66; 77)	71 (66; 76)	72 (67; 78)
Cardiac rate, bpm			
Mean (SD)	67 (11.3)	65.6 (9.4)	67 (9.6)
Median (25°; 75°)	65 (59; 75)	64 (61; 72)	66 (61; 73)
Respiratory rate, cpm			
Mean (SD)	16.2 (3)	16.6 (2.5)	16 (2.3)
Median (25°; 75°)	16 (14; 18)	16 (16; 18)	16 (14; 18)
VAS of anxiety			
Mean (SD)	1.2 (1.4)	1.0 (1.2)	1.3 (1.5)
Median (25°; 75°)	0.7 (0.2; 1.8)	0.7 (0.2; 1.5)	0.9 (0.4; 1.8)
STAI-S			
Mean (SD)	27.6 (7.4)	27.5 (6.4)	29.8 (7.0)
Median (25°; 75°)	26 (22; 31)	26 (23; 30)	28 (24; 34.5)
EEAC, self-confidence			
Mean (SD)	30.4 (5.7)	30 (4.1)	30.1 (4.5)
Median (25°; 75°)	32 (28; 35)	30 (27; 33)	30 (27; 34)
EEAC, cognitive anxiety			
Mean (SD)	9.4 (3.5)	10.2 (3.6)	10.2 (3.2)
Median (25°; 75°)	8 (7; 11)	9 (7; 12)	9 (8; 12)
EEAC, somatic anxiety			
Mean (SD)	9.5 (3.3)	9.5 (2.7)	9.9 (3.3)
Median (25°; 75°)	8 (7; 11)	9 (7; 11)	9 (7; 12)

CH, centesimal hahnemannian; EEAC, evaluation de l'Etat d'Anxiété à la compétition; STAI, state-trait anxiety inventory; STAI-T, trait part of state-trait anxiety inventory; VAS, visual analogical scale; Bpm, battements per minute; Cpm, cycles per minute.

[a]STAI-T, the threshold was 35.55 for men and 36.15 for women.

aration of *Argentum Nitricum* 12DH and placebo. The authors also used the Test Anxiety Scale. The quality of this second study was good, with a calculation of its power that was acceptable. However, contrary to Stanton [22], they found no significant difference between the three groups for the values of test anxiety.

Among homeopathic remedies, *Gelsemium* is commonly prescribed by homeopaths to prevent anticipatory anxiety. However, scientific evidence for such prescription is lacking, given the fact that no randomized clinical trial has been performed to test its efficacy. In addition, whilst meta-analyses performed in 2007 by Shang [24] do not support an effect of homeopathy, other meta-analyses of clinical trials evaluating the effectiveness of homeopathic medicines concluded that available evidence was positive but not sufficient to draw definitive conclusion [25,26]. Specific reviews remain inconclusive too [21]. Therefore, in our present study, we wanted to reproduce a situation of stress induced by a specific event. Such an experimental set-up has already been

Table II Opinions about homeopathy at enrolment.

	Gelsemium 15CH (n = 59)	*Gelsemium* 5CH (n = 61)	Placebo (n = 60)
Do you know about homeopathy? Yes, *n/N* (%)	55/58 (94.8)	59/61 (96.7)	56/60 (93.3)
Have you previously used homeopathic therapy? Yes, *n/N* (%)	40/58 (68.9)	53/61 (86.9)	48/60 (80)
If Yes: For anxiety? Yes, *n/N* (%)	13/55 (23.6)	19/61 (31.1)	23/58 (39.7)
For any other indication? Yes, *n/N* (%)	36/56 (64.3)	50/61 (82.0)	45/58 (77.6)
Do you think that homeopathic therapy is efficient for anxiety?			
No, *n/N* (%)	6/58 (10.3)	10/61 (10.4)	14/60 (23.3)
Yes, *n/N* (%)	35/58 (60.4)	34/61 (55.7)	34/60 (56.7)
No opinion, *n/N* (%)	17/58 (29.3)	17/61 (27.9)	12/60 (20.0)
Do you think that homeopathic therapy will help you to feel less anxious during the test that you will take?			
No, *n/N* (%)	17/58 (29.3)	15/61 (24.6)	20/60 (33.3)
Yes, *n/N* (%)	19/58 (32.8)	30/61 (49.2)	23/60 (38.4)
No opinion, *n/N* (%)	22/58 (37.9)	16/61 (26.2)	17/60 (28.3)

CH, centesimal hahnemannian; DNK, do not know. Data are given as percentages. No statistical signification.

Table III Score of STAI-S, VAS and EEAC at baseline and before the SCWT.

	Gelsemium 15CH (n = 58)	*Gelsemium* 5CH (n = 61)	Placebo (n = 60)	*P*
Score STAI-S				
Baseline, mean (SD)	27.8 (7.2)	28.6 (8.0)	29.8 (7.8)	0.37
Before SCWT, mean (SD)	29.6 (8.2)	29.6 (6.7)	31.1 (8.1)	0.44
D0–Basal, mean (SD)	1.8 (6.0)	1.0 (6.3)	1.4 (6.4)	0.80
CI 95%	[0.2 to 3.4]	[−0.6 to 2.6]	[−0.3 to 3.0]	
Effect size	0.2	0.1	0.2	
Anxiety VAS				
Baseline, mean (SD)	0.9 (1.2)	0.9 (1.0)	1.1 (1.2)	0.38
Before SCWT, mean (SD)	1.7 (1.6)	1.6 (1.3)	1.8 (1.3)	0.69
D0–Basal, mean (SD)	0.7 (1.1)	0.7 (1.2)	0.7 (1.1)	0.94
CI 95%				
Score EEAC-1 (self-confidence)				
Baseline, mean (SD)	30.9 (4.9)	29.9 (5.0)	30.1 (4.5)	0.48
Before SCWT, mean (SD)	30.4 (5.6)	29.2 (4.9)	29.5 (5.0)	0.43
D0–Basal, mean (SD)	−0.5 (3.5)	−0.7 (3.1)	−0.6 (3.5)	0.96
CI 95%	[−1.4 to 0.4]	[−1.5 to 0.1]	[−1.5 to 0.3]	
Score EEAC-2 (cognitive anxiety)				
Baseline, mean (SD)	9.5 (3.4)	10.7 (3.7)	10.3 (3.3)	0.16
Before SCWT, mean (SD)	9.0 (2.9)	9.9 (2.9)	9.5 (2.7)	0.22
D0–(D-2 or D-7), mean (SD)	−0.5 (2.5)	−0.8 (3.0)	−0.7 (3.0)	0.82
CI 95%	[−1.2 to 0.1]	[−1.6 to −0.1]	[−1.5 to 0.0]	
Score EEAC-3 (somatic anxiety)				
Baseline, mean (SD)	9.1 (2.7)	9.5 (2.7)	9.2 (2.5)	0.59
Before SCWT, mean (SD)	10.7 (3.6)	10.6 (2.8)	11.4 (3.7)	0.39
D0–(D-2 or D-7), mean (SD)	1.7 (3.2)	1.1 (3.5)	2.3 (3.6)	0.17
CI 95%	[0.8 to 2.5]	[0.2 to 2.0]	[1.3 to 3.2]	

STAI-S, state part of the state-trait anxiety inventory; VAS, visual analogical scale; EEAC, Evaluation de l'Etat d'Anxieté à la Compétition; D0, Day 0, just before the SCWT; D-2, Baseline (at home); D-7, basal if D-2 not available; SCWT, Stroop colour word test; SD, standard deviation; CI, confidence interval; CH, centesimal hahnemannian.

used to test standard pharmacological treatments such as Diazepam. The major pitfall is that the tests used in the experimental design do not correspond to real life. However, these experimental set-ups with large groups enabled many confounding biases to be controlled in a 'proof of concept' study. Our test was performed according to previous reports, which demonstrated that a Stroop colour test could be stressful under specific conditions. In our study, the baseline score of STAI-S at the beginning of visit V2 was lower than expected, but rose before the Stroop colour test [13]. One potential bias of our study is that this provocative stress test is not only sensitive to stress but also to attention and motivation. However, whilst other tests can be used to provoke anxiety [7–9], they are either difficult to use, non-reproducible or non-ethical.

Furthermore, the STAI-S score increased during the test to reach a maximum value in the middle of the test and decreased rapidly thereafter. The stressful properties of the test were further supported by the anxiety VAS results. Objective sympathetic activation also occurred, as shown by increased mean blood pressure and heart rate. The complete scenario played-out to stress the volunteer when they arrived for visit V2 was in fact stressful as the STAI-S score increased, but was less stressful than the SCWT itself. However, detailed analysis showed that none of the treatments affected any clinical parameter during the test.

As a large number of students were included, our study population was representative of a real life population that is confronted with anticipated anxiety. But we did not assess the personality of this population and we cannot demonstrate that it is fully representative of the target population of homeopathy. This population

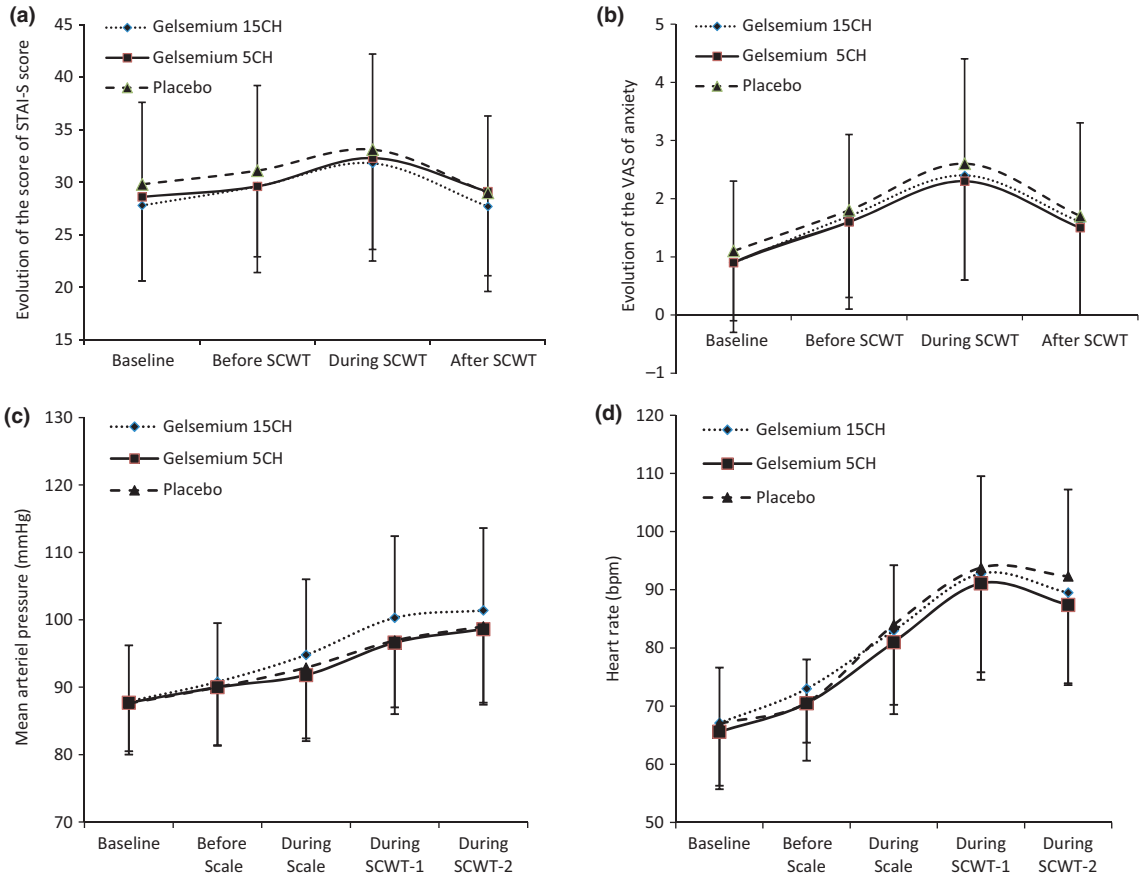

Figure 2 Evolution of State-Trait Anxiety Inventory (STAI-S), visual analogical scale (VAS) of anxiety, mean arterial pressure and heart rate during the V2 study. (a) Evolution of STAI-S. SCWT: Stroop colour word test. Baseline values of STAI-S measured at home; before: values of STAI-S measured before the beginning of the first part of the SCWT; during SCWT: values of STAI-S measured between the two parts of the SCWT. After SCWT: values of STAI-S measured at the end of the SCWT. (b) Evolution of VAS of anxiety. Baseline: values of VAS of anxiety measured at home; Before: values of VAS of anxiety measured before the beginning of the first part of the SCWT; During SCWT: values of VAS of anxiety measured between the two parts of the SCWT. After SCWT: values of VAS of anxiety measured at the end of the SCWT. (c) Evolution of the mean arterial pressure during the V2 study. Baseline: values of arterial blood pressure measured at the beginning of the visit; before scale: values of arterial blood pressure measured up to when the subject began to fill in the first VAS, Evaluation de l'Etat d'Anxiété à la Compétition (EEAC) and STAI-S scale; during scale: values of arterial blood pressure recorded whilst the subject filled in the scales. During SCWT-1: values of arterial blood pressure measured during the first part of the SCWT. During SCWT-2: values of arterial blood pressure measured during the second part of the SCWT. (d) Evolution of the heart rate during the V2 study. Bpm, battements per minute. Baseline: values of heart rate measured at the beginning of the visit; before scale: values of heart rate measured up to when the subject began to fill in the first VAS, EEAC and STAI-S scale; during scale: values of heart rate recorded whilst the subject filled in the scales. During SCWT-1: values of heart rate measured during the first part of the SCWT. During SCWT-2: values of heart rate measured during the second part of the SCWT.

was stratified based on their STAI-T score, but subgroup analysis showed no differences between groups for those with higher STAI-T values.

Given the lack of guidelines, the choice of the homeopathic medicine and the treatment duration was performed after discussion with homeopathic general practitioner. Therefore, whether we chose the most appropriate homeopathic treatment should be discussed. In general practice, *Gelsemium* (or indeed most other homeopathic treatments) is generally prescribed in combination with other homeopathic medicine. To avoid confusion, we chose to test the single agent most commonly prescribed for anxiety. The treatment duration was determined by the homeopath consulted. However, this duration (48 h) was relatively short; the duration is a variable which may probably influence treatment response. Long duration of homeopathic treatment more than 2 days may have been more

beneficial. As discussed in our previous study on homeopathic treatment for pain following knee ligament reconstruction [27], the usual mode of prescription of homeopathy is difficult to reproduce in a randomized clinical trial vs. placebo, because for the same pathology the treatment prescription can differ between patients, depending of the symptoms described; the prescription of homeopathic treatments being highly personalized.

CONCLUSION

Gelsemium 5CH or 15CH do not prevent anticipatory anxiety in healthy volunteers, in the conditions used in our study.

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CONFLICTS OF INTEREST, FUNDING AND ETHICAL COMMITTEE APPROVAL

Boiron financially supported the project, provided the treatments but did not take legal responsibility for the study, which was sponsored by Grenoble University Hospital. They did not participate in realization of the study or in data analysis and interpretation. The protocol and the informed consent form were approved by the French ethics committee ('Comité de protection des personnes Sud-Est V') on 13 May 2009.

ABBREVIATIONS LIST

AE – adverse event
CH – centesimal hahnemannian
CSAI-2 – competitive state anxiety inventory-2
DH – decimal hahnemannian
EEAC – evaluation de l'Etat d'Anxiété à la compétition
SCWT – Stroop Colour Word Test
STAI-S – state part of state-trait anxiety inventory
STAI-T – trait part of state-trait anxiety inventory
VAS – visual analogical scale

REFERENCES

1 Cattell R., Scheier I. The meaning and measurement of neuroticism and anxiety, Ronald Press Co., New York, 1961.
2 Spielberger C. Anxiety and behavior. Academic Press, New York, 1966.
3 Bousta D., Soulimani R., Jarmouni I. et al. Neurotropic, immunological and gastric effects of low doses of *Atropa belladonna* L., *Gelsemium sempervirens* L. and Poumon histamine in stressed mice. J. Ethnopharmacol. (2001) **74** 205–215.
4 Magnani P., Conforti A., Zanolin E., Marzotto M., Bellavite P. Dose-effect study of *Gelsemium sempervirens* in high dilutions on anxiety-related responses in mice. Psychopharmacology (Berl.) (2010) **210** 533–545.
5 Venard C., Boujedaini N., Belon P., Mensah-Nyagan A.G., Patte-Mensah C. Regulation of neurosteroid allopregnanolone biosynthesis in the rat spinal cord by glycine and the alkaloidal analogs strychnine and gelsemine. Neuroscience (2008) **153** 154–161.
6 Venard C., Boujedaini N., Mensah-Nyagan A.G., Patte-Mensah C. Comparative analysis of gelsemine and *Gelsemium sempervirens* activity on neurosteroid allopregnanolone formation in the spinal cord and limbic system. Evid. Based Complement Alternat. Med. (2009) **23** 1–9.
7 Geeraerts B., Vandenberghe J., Van Oudenhove L. et al. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. Gastroenterology (2005) **129** 1437–1444.
8 Lu K., Gray M.A., Oliver C. et al. The acute effects of L-theanine in comparison with alprazolam on anticipatory anxiety in humans. Hum. Psychopharmacol. (2004) **19** 457–465.
9 Schumacher R., Velden M. Anxiety, pain experience, and pain report: a signal-detection study. Percept. Mot. Skills (1984) **58** 339–349.
10 Tulen J.H., Moleman P., van Steenis H.G., Boomsma F. Characterization of stress reactions to the Stroop Color Word Test. Pharmacol. Biochem. Behav. (1989) **32** 9–15.
11 Tulen J.H., Moleman P., Boomsma F., van Steenis H.G., van den Heuij V.J. Dose-dependent effects of intravenous lorazepam on cardiovascular activity, plasma catecholamines and psychological function during rest and mental stress. Psychopharmacology (Berl.) (1991) **105** 77–83.
12 Graeff F.G., Parente A., Del-Ben C.M., Guimaraes F.S. Pharmacology of human experimental anxiety. Braz. J. Med. Biol. Res. (2003) **36** 421–432.
13 Teixeira-Silva F., Prado G.B., Ribeiro L.C., Leite J.R. The anxiogenic video-recorded Stroop Color-Word Test: psychological and physiological alterations and effects of diazepam. Physiol. Behav. (2004) **82** 215–230.
14 Putman P., Hermans E.J., Koppeschaar H., van Schijndel A., van Honk J. A single administration of cortisol acutely reduces preconscious attention for fear in anxious young men. Psychoneuroendocrinology (2007) **32** 793–802.
15 Leite J.R., Seabra Mde L., Sartori V.A., Andreatini R. The video-recorded Stroop Color-Word Test as a new model of

experimentally-induced anxiety. Prog. Neuropsychopharmacol. Biol. Psychiatry (1999) **23** 809–822.
16 Boutcher Y.N., Boutcher S.H. Cardiovascular response to Stroop: effect of verbal response and task difficulty. Biol. Psychol. (2006) **73** 235–241.
17 Bruchon-Schweitzer M., Paulhan I. Adaptation française de l'Inventaire d'Anxiété Trait-Etat. Forme Y (STAI Y), Les Éditions du Centre de Psychologie Appliquée ed, Paris, 1993.
18 Cury P., Sarrazin P., Peres C., Famose J. Mesurer l'anxiété du sportif en compétition: présentation de l'échelle d'état d'anxiété en compétition (EEAC). La gestion du Stress. Dossier EPS no 43, Revue EPS, Paris, 1999.
19 Martens R., Burton D., Vealey R., Bump L., Smith D. Development and validation of the competitive state anxiety inventory-2 (CSAI-2). Competitive anxiety in sport. Human Kinetics, Publisher Inc., Champaign, 1990, pp. 117–190.
20 Eisenberg D.M., Davis R.B., Ettner S.L. et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. JAMA (1998) **280** 1569–1575.
21 Pilkington K., Kirkwood G., Rampes H., Fisher P., Richardson J. Homeopathy for anxiety and anxiety disorders: a systematic review of the research. Homeopathy (2006) **95** 151–162.
22 Stanton H. Test anxiety – a five drop solution. Educ. News (1981) **17** 12–15.
23 Baker D.G., Myers S.P., Howden I., Brooks L. The effects of homeopathic Argentum nitricum on test anxiety. Complement Ther. Med. (2003) **11** 65–71.
24 Shang A., Huwiler-Muntener K., Nartey L. et al. Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. Lancet (2005) **366** 726–732.
25 Kleijnen J., Knipschild P., ter Riet G. Clinical trials of homoeopathy. BMJ (1991) **302** 316–323.
26 Linde K., Clausius N., Ramirez G. et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet (1997) **350** 834–843.
27 Paris A., Gonnet N., Chaussard C. et al. Effect of homeopathy on analgesic intake following knee ligament reconstruction: a phase III monocentre randomized placebo controlled study. Br. J. Clin. Pharmacol. (2008) **65** 180–187.