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Phase II trial on the effects of Silexan in patients with neurasthenia, post-traumatic stress disorder or somatization disorder

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ABSTRACT

Silexan, a novel lavender oil preparation for oral use, has been authorized in Germany for the treatment of states of restlessness during anxious mood. An open-label, exploratory trial was performed to assess the potential of the medicinal product in the treatment of restlessness caused by anxiety as related to several disorders. Outcome measures included the Symptom Checklist-90-Revised (SCL-90-R), von Zerssen's Depression Scale (D-S), the 36-item Short Form Health Survey Questionnaire (SF-36), and a sleep diary.

50 male and female patients with neurasthenia (ICD-10 F48.0), post-traumatic stress disorder (PSD; F43.1), or somatization disorder (F45.0, F45.1) were included to receive 1 × 80 mg/day Silexan over 6 weeks; 47 could be analyzed for efficacy as full analysis set. At baseline, patients suffered from restlessness (96%), depressed mood (98%), sleep disturbances (92%), or anxiety (72%). Of those, resp. 62%, resp. 57%, resp.51%, resp. 62% showed improvements during treatment ($p < 0.001$). For all patients, mean D-S score decreased by 32.7% and SCL-90-R Global Severity Index by 36.4% as compared to baseline, ($p < 0.001$), while the SF-36 Mental Health Score increased by 48.2% ($p < 0.001$). Waking-up frequency ($p = 0.002$), Waking-up duration ($p < 0.001$) and morning tiredness ($p = 0.005$) were reduced, while efficiency of sleep ($p = 0.018$) and mood ($p = 0.03$) improved. Patients suffering from neurasthenia or PSD showed comparable improvements with most outcomes.

The results in this trial justify to further investigate Silexan in disorders with accompanying restlessness caused by sub-threshold anxiety. Adverse reactions, predominantly gastrointestinal complaints, were judged as mild or moderate.

Introduction

Lavender oil contains more than 160 substances including linalool, linalyl acetate, 1.8-cineole, β-ocimene, terpinen-4-ol and camphor as main constituents. Therapeutic effects of these constituents in man have been investigated only as part of differently produced whole extracts containing these constituents in different concentrations (Cavanagh and Wilkinson 2002).

Systematic scientific research into the effects of lavender oil has been initiated during recent decades. Psychiatric and psychological studies in patients indicate that lavender oil has relaxing (Field et al. 2005; Hardy et al. 1995; Motomura et al. 2001; Wolfe and Herzberg 1996) as well as anxiolytic properties (Bradley et al. 2009; Kritsidima et al. 2010; Lehrner et al. 2005; Louis and Kowalski 2002; Woelk and Schlaefke 2010) and antidepressant effects (Akhondzadeh et al. 2003; Louis and Kowalski 2002). Furthermore, the herbal remedy has been shown to have a beneficial effect on mood and general well-being (Knasko 1992; Lehrner et al. 2005; Louis and Kowalski 2002; Uehleke 1996; Vernet-Maury et al. 1999).

Silexan[1] is a patented active substance with an essential oil produced from *Lavandula angustifolia* flowers that has been licensed in Germany as herbal medicinal product for the treatment of states of restlessness during anxious mood after the completion of the study. In a double-blind, double dummy randomized clinical trial, Woelk and Schlaefke (2010) compared anxiolytic efficacy of 80 mg Silexan and 0.5 mg lorazepam once daily in 77 patients with generalized

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[1] Silexan® is the active substance of LASEA® (W. Spitzner Arzneimittelfabrik GmbH, Ettlingen).

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anxiety disorder (GAD) under the hypothesis of non-inferiority of the herbal preparation. During 6 weeks of treatment, total score of the Hamilton Anxiety Scale (HAMA; Hamilton 1976) as primary outcome measure decreased by 11.3 ± 6.7 units (mean ± *SD*) or 45% of the baseline value in the Silexan group and by 11.6 ± 6.6 units or 46% in the lorazepam group. Adverse events with a potential causal relationship to Silexan were nausea, eructation, and dyspepsia. The authors concluded that Silexan is safe and has an anxiolytic potential like lorazepam at standard dosage of 0.5 mg/day.

This research suggests that Silexan may be beneficial in symptoms of anxiety as familiarized with several further disorders. We decided to investigate into sub-threshold anxiety (Volz et al. 2011) in relation to neurasthenia, post-traumatic stress disorder (PSD) and somatization disorder. According to the definitions of the World Health Organization (WHO 1992), neurasthenia is characterized by feelings of weakness and fatigue after mental or physical effort that are associated with difficulties to concentrate, generally inefficient thinking, feeling of muscular pain and inability to relax. Neurasthenic patients tend to experience a variety of other symptoms, such as dizziness, tension headaches, and feelings of general instability. Worry about decrease of mental and physical well-being is common.

In post-traumatic stress disorder, typical features include flashback episodes of the trauma, dreams or nightmares, occurring against the persisting background of a sense of emotional "numbness" or blunting, detachment from the social environment, and avoidance of activities and situations reminiscent of the trauma. There is usually a state of autonomic hyperarousal with hypervigilance. Features common to both conditions include anhedonia and varying degrees of depression and anxiety as well as disturbed sleep.

Materials and methods

Design

During this open-label exploratory trial, all patients included received Silexan during the scheduled treatment period of 6 weeks. The protocol included visits at baseline, weeks 1, 3, and 6. The trial was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki. An independent ethics committee (Charité University Medicine) reviewed and approved the trial protocol. All patients gave their written informed consent. Clinical monitoring was performed at regular intervals according to the requirements of Good Clinical Practice.

Patients

The trial was performed in a single secondary care center in Germany. Male and female out-patients between 18 and 70 years of age who suffered from either neurasthenia (ICD10 F48.0), post-traumatic stress disorder (PSD, F43.1) or somatization disorder (F45.0, F45.1) (WHO 1992), and who had not been treated for these disorders for at least 3 months, were eligible for inclusion. Diagnosis was established in accordance with the DSM-IV manual either by previous written reports from a specialist in psychiatry or psychosomatic medicine or by a specialist in the trial center during recruitment. Acute symptom load was estimated by a minimum score of two points ('sometimes') for at least two of the four items of the State Check Questionnaire (restlessness, anxiety, sleep disturbance, depressed mood; see below). Female patients of childbearing potential had to have a negative pregnancy test and had to use adequate contraception. Patients of any ethnic group were eligible for participation. Patients suffering from any other psychiatric or neurological disorders as well as those with a relevant progressive disease were excluded from participation. Any psychotropic drugs other than the investigational treatment, any long-term prophylactic treatment, centrally acting antihypertensives, anti-Parkinson medication, muscle relaxants, anaesthetics or analgesics of opiate type were not allowed as concomitant medication. Furthermore, patients undergoing short-term (<6 months) psychotherapy during the last 2 months prior to inclusion were ineligible for participation, while ongoing long-term psychotherapy (>6 months) was possible.

Treatment

Silexan is available in immediate release soft gelatine capsules containing 80 mg of lavender oil. It complies with the monograph Lavender oil of the European Pharmacopeia and exceeds the quality definition of the pharmacopoeial monograph with respect to items important for efficacy and tolerability. The uniformity of the specific composition of Silexan is warranted by continuous quality controls.

All trial patients had to take one unchewed capsule a day over 6 weeks. The individual time of administration depended on the results of the State Check Questionnaire with respect to sleep quality, and the time of the day at which the symptoms predominantly occurred. The investigator was free to adjust the time of administration at each visit if felt advisable.

Outcome measures

The following scales were used as efficacy outcome measures: Symptom Checklist-90-Revised (SCL-90-R; Derogatis 1994) is a 90-Item Self-Report Inventory that is subdivided into nine dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism) from which a Global Severity Index can be calculated. The State-Trait Anxiety Inventory (STAI; Kendall et al. 1976) was administered as a self-report measure of state and trait anxiety. The von Zerssen's Depression Scale (D-S; Von Zerssen et al. 1974) was used as a self-report of depression. The Maslach Burnout Inventory (MBI; Maslach and Jackson 1981) was designed as a self-rating instrument to assess emotional exhaustion, depersonalization, and reduced personal accomplishment as contributing factors of the burnout syndrome. General health concepts were investigated using the 36-item Short Form Health Survey Questionnaire (SF-36; Ware and Sherbourne 1992). The State Check is a simple, self-reported, four-item measure of restlessness, impaired sleep, depressed mood, and anxiety. The set of efficacy assessments was completed by a validated sleep diary (Hoffmann et al. 1997) assessing mood (morning/evening), tiredness (morning/evening), sleep efficiency and latency, frequency and duration of waking up as well as total bed time and sleep time. Data of sleep diary recorded during the first week of treatment were used as baseline values. Safety and tolerability were assessed based on spontaneous reports of adverse events (AEs), asked for at each visit. Furthermore, vital signs were recorded at baseline and after 3 and 6 weeks, while physical and ECG examinations and routine laboratory measurements were performed at baseline and after 6 weeks.

Statistical methods, sample size

Biometric analysis was limited to descriptive statistics. For demographic, effect and safety measures statistics characterizing the empirical distributions of data were computed and confidence intervals as well as descriptive p-values for change over time were determined. Figs. 2 and 3 present standardized mean values for change versus baseline within the diagnostic groups that were computed as $\text{mean}_{ST} = (\text{mean}_{OBS}/SD) \times \sqrt{n}$, where mean_{ST} is the standardized mean value, mean_{OBS} is the observed mean value, *SD* is the observed standard deviation and *n* is the sample size within

the group of interest. These standardized mean values correspond to the t statistic of the one sample t-test that is distributed with $n-1$ degrees of freedom, and thus standardized mean values of about ± 2.2 represent a descriptively significant change versus baseline at the two-sided $\alpha = 0.05$ error level (depending on subgroup sample size).

Missing values were replaced by carrying the last observation forward (LOCF).

The primary analysis was based on the full analysis set (FAS) that included all patients who received at least one dose of trial medication and who had at least one post baseline outcome assessment of the SCL-90-R, the STAI, the D-S, the MBI, or the SF-36. An additional per protocol (PP) analysis was performed as a sensitivity analysis. All p-values are two-sided.

A sample size of 50 patients was regarded as appropriate based on clinical considerations.

Results

Patients, patient accountability, analysis data sets

50 patients (42 female) were included. 10 patients terminated their participation before the scheduled end. Reasons for premature withdrawal were adverse events (5 patients), non-response (2), withdrawal of consent, participation in another trial, and non-attendance at visits due to vacations (1 each). 3 of these patients did not provide any post-baseline data. Thus 47 patients (mean age 51.6 years, range 28–65 years) could be included in the FAS.

Relevant protocol violations which could bias the assessment of the treatment effect were observed in 4 patients included in the FAS (2 treatment compliance <80%, 1 newly introduced psychotropic co-medication, 1 discontinuation after less than 80% of the scheduled trial period for reasons not related to the treatment effect or to tolerability). Thus 43 patients were included in the PP analysis.

Baseline data, treatment compliance

Table 1 shows baseline demographic data and diagnoses at inclusion. More than 80% of the patients were female. The most frequent underlying disease was PSD without accompanying neurasthenia. 6 of the 9 patients with the leading diagnosis somatization disorder also suffered from neurasthenia or PSD. The most frequent non-psychiatric concomitant diseases were related to ocular disorders (32 patients, 68.1%), musculoskeletal and connective tissue disorders (24, 51.1%) and infectious diseases (22, 46.8%). All patients were Caucasians although this was not a criterion for inclusion.

Table 1
Baseline characteristics (full analysis set, $n = 47$; absolute and relative (%) frequencies; mean ± *SD*).

Sex	
Female	39 (83.0%)
Male	8 (17.0%)
Age (years)	51.6 ± 8.8
Height (cm)	169.4 ± 7.9
Weight (kg)	71.6 ± 12.4
Diagnosis (multiple responses)	
Neurasthenia (without post-traumatic stress disorder)	14 (29.8%)
Post-traumatic stress disorder (without neurasthenia)	17 (36.2%)
Neurasthenia + post-traumatic stress disorder	13 (27.7%)
Somatization disorder (with or without post-traumatic stress disorder or neurasthenia)	9 (19.1%)

Clinical effects

Table 2 shows the number of patients who suffered from symptoms of restlessness, anxiety, disturbed sleep, and depressed mood according to the State Check Inventory. By the end of the treatment period, hints for effects were found in 29 of the 45 patients (64.4%) affected at baseline with restlessness, in 21 of 34 (61.8%) with anxiety, in 24 of 43 (55.8%) with sleep disturbances, and in 27 of 46 patients (58.7%) with depression.

Table 3 presents the results of the selected scales. After 6 weeks of treatment, the most pronounced improvements were observed for the mean value of the SF-36 mental health subscore (+48.2% as compared to baseline). Significant improvements were observed for all SF-36 subscales except bodily pain and general health (one-sided Wilcoxon signed rank test: physical functioning $p < 0.001$, role physical $p = 0.018$, bodily pain $p = 0.035$ general health $p = 0.123$, vitality $p < 0.001$, social functioning $p < 0.001$, role emotional $p < 0.001$, mental health $p < 0.001$, reported health transition $p = 0.002$).

Depression Scale was improved by 32.7 and SCL-90-R Global Severity Index by 36.4%, where significant symptom ameliorations were observed in each of the nine subscales (all $p < 0.001$) as well as for global measures (Global Severity Index, Positive Symptom Total and Positive Symptom Distress Index). For state and trait anxiety (STAI), the observed improvements were moderate albeit significant. The items of the sleep diary indicate that compared to baseline, patients reported an increase in total sleep time ($p = 0.04$, Wilcoxon test) despite slightly reduced bed time. Waking-up frequency ($p = 0.002$) and waking-up duration ($p < 0.001$) were reduced and sleep efficiency was improved ($p = 0.018$) so that the trial patients were on average less tired ($p = 0.005$) and in a better mood ($p = 0.03$) in the morning.

The summary measures of the MBI indicate a systematic reduction of emotional exhaustion whereas only minor changes were observed for reduced personal accomplishment and depersonalization associated with burnout syndrome.

To assess the clinical effects of Silexan in the conditions of interest, subgroup analyses broken down by diagnosis at trial inclusion were performed. Fig. 1 shows the patients' change from baseline during treatment with lavender oil for the items of the State Check. For restlessness, disturbed sleep and depressed mood the percentages of patients with different underlying diseases whose symptoms appeared sometimes, often or always at baseline ranged between 92.3% and 100.0%, between 82.3% and 100.0%, and between 92.3% and 100.0%, respectively. On the other hand, anxiety at baseline was more frequent in patients with neurasthenia (about 85%; with or without accompanying PSD) than in those with PSD alone (58.8%). A notably large percentage of patients with neurasthenia (but without PSD) reported relief from symptoms of restlessness. Anxiety, on the other hand, showed the highest rate of improvement in patients suffering from a combination of neurasthenia and PSD. For the one-item measures of sleep disturbances and depressed mood the differences between the underlying diseases were less pronounced.

According to the data presented in Fig. 2 patients with neurasthenia or PSD alone showed a marked decrease of nocturnal waking up frequency and duration after 6 weeks of treatment with Silexan. In patients suffering from neurasthenia (with or without accompanying PSD) morning mood and tiredness as well as sleep efficiency were also substantially improved, and all patients showed an increase in nighttime but not in daytime sleep. On the other hand, sleep latency was increased in trial patients suffering from PSD (with or without neurasthenia).

At baseline patients suffering from PSD only had consistently lower total scores and subscores in the STAI, the D-S and the SCL-90-R than trial patients with neurasthenia (with or without PSD).

Table 2
State Check at baseline and after treatment (full analysis set, $n = 47$).

Item	Baseline: symptom frequency, n (%) "sometimes", "often" or "mostly/always"	Day 42: frequency "improved", n (%)	p-Value[#] for change between baseline and day 42
Restlessness	45 (95.7%)	29 (61.7%)	<0.001
Anxiety	34 (72.3%)	21 (44.7%)	<0.001
Sleep disturbances	43 (91.5%)	24 (51.1%)	<0.001
Depressed mood	46 (97.9%)	27 (57.4%)	<0.001

[#] Wilcoxon signed rank test performed on the difference of original item values between baseline and day 42.

Table 3
Clinical outcome measures at baseline and treatment end (full analysis set, $n = 47$; mean ± SD and % change of mean value).

Scale	Baseline	Absolute change, Day 42 – baseline	Relative change (%)	p-Value[#] for change between baseline and Day 42
State-Trait Anxiety Inventory				
State anxiety	46.2 ± 10.8	−4.5 ± 10.7 ($n = 46$)	−9.7%	0.005
Trait anxiety	53.9 ± 7.8	−7.4 ± 8.9 ($n = 46$)	−13.7%	<0.001
Depression Scale (total score)	15.9 ± 7.5	−5.2 ± 6.9 ($n = 46$)	−32.7%	<0.001
Symptom Checklist-90-Revised				
Global Severity Index	1.1 ± 0.5	−0.4 ± 0.3	−36.4%	<0.001
Positive Symptom Total	51.5 ± 15.0	−13.1 ± 12.2	−25.4%	<0.001
Positive Symptom Distress Index	1.8 ± 0.4	−0.4 ± 0.4	−22.2%	<0.001
36 Item Short Form Health Survey				
Total score – physical health	60.2 ± 20.3	8.3 ± 16.6	+13.8%	<0.001
Total score – mental health	39.0 ± 15.5	18.8 ± 22.3	+48.2%	<0.001
Maslach Burnout Inventory				
Emotional exhaustion	3.8 ± 1.5	−0.7 ± 1.0	−18.4%	<0.001
Reduced personal accomplishment	4.2 ± 1.2	0.2 ± 1.0	+4.8%	0.285
Depersonalization	2.6 ± 1.6	−0.2 ± 1.3	−7.7%	0.538

[#] Wilcoxon signed rank test.

In case of the SCL-90-R this applied to all subscales except somatization.

Table 4 presents the main results for STAI and D-S. For trait anxiety the diagnostic subsets showed average improvements by 10.7% for patients with PSD only, by 13.4% for those with neurasthenia only, and by and 15.7% for study participants with neurasthenia and PSD as compared to baseline. Except for patients with comorbidity of neurasthenia and PSD, average improvements of state anxiety were less pronounced. The average total score of D-S improved by 24.8% for PSD only, 33.3% for neurasthenia only, and by 29.5% for patients with comorbidity of neurasthenia and PSD as compared to baseline.

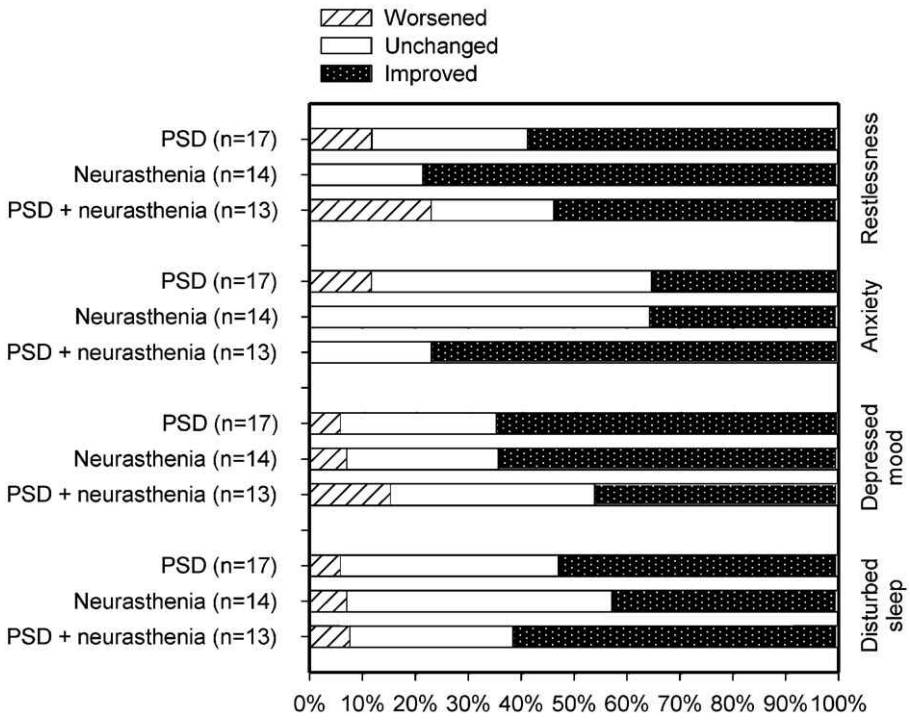

Fig. 1. State Check – change between status at baseline and at day 42, given by underlying disease (full analysis set; PSD: post-traumatic stress disorder).

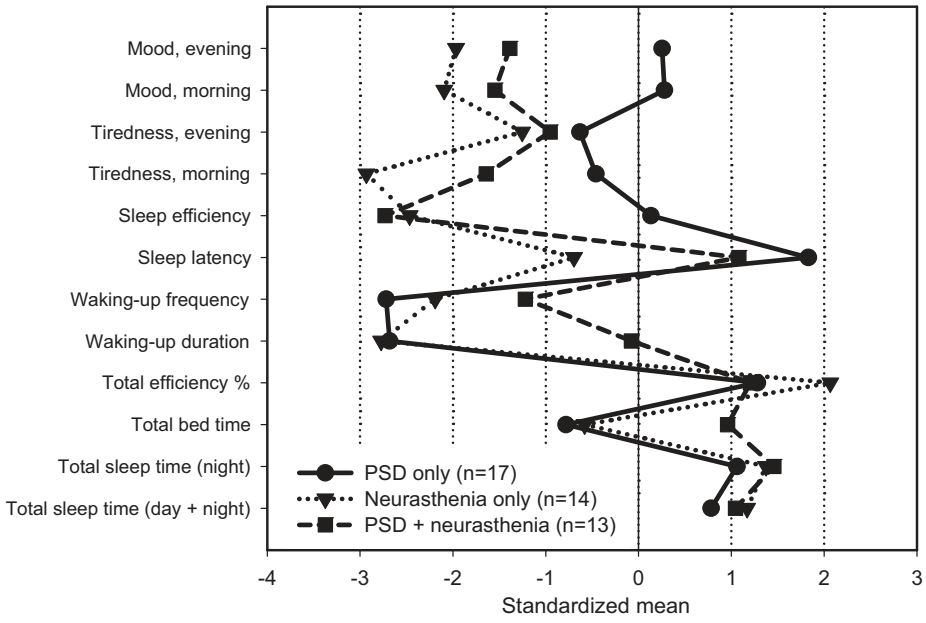

Fig. 2. Sleep diary – change between baseline and day 42 by underlying disease (full analysis set; negative values denote improvement, PSD: post-traumatic stress disorder).

Table 4
State-Trait Anxiety Inventory and depression scale summary scores: Baseline value and percent improvement at day 42, by underlying disease (full analysis set; mean ± *SD*).

		Neurasthenia only ($n = 14$)	PSD only ($n = 17$)	Neurasthenia + PSD ($n = 13$)
State anxiety	Baseline	47.5 ± 11.9	43.4 ± 11.3	48.9 ± 9.8
	Improvement	7.5% ± 28.0%	2.7% ± 18.1%	16.7% ± 23.7%
Trait anxiety	Baseline	56.2 ± 7.1	49.9 ± 8.2	56.0 ± 7.0
	Improvement	13.4% ± 17.7%	10.7% ± 12.2%	15.7% ± 17.8%
Depression Scale	Baseline	19.9 ± 8.2	12.8 ± 5.9	16.6 ± 7.6
	Improvement	33.6% ± 26.0%	24.8% ± 37.3%	29.5% ± 36.2%

Fig. 3 shows significant amelioration of the symptoms assessed by means of the SCL-90-R in patients with neurasthenia (7 out of the scale's 9 primary symptom dimensions), PSD (7 out of 9 dimensions), or neurasthenia and PSD comorbidity (all dimensions). Furthermore, each of the three subsets of patients showed significant improvements in the scale's global indices (Global Severity Index, Positive Symptom Total, Positive Symptom Distress Index; standardized mean values <−2.2 were considered descriptively significant).

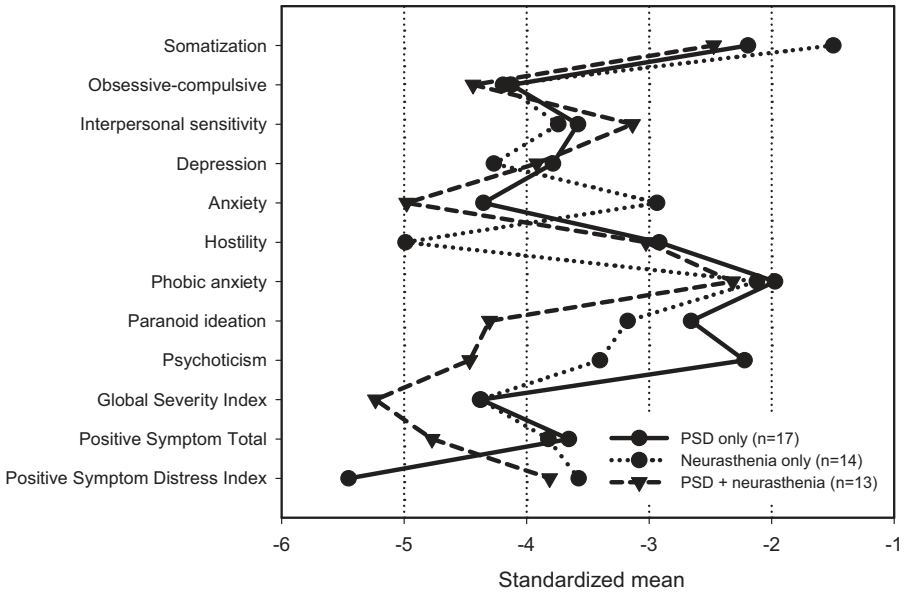

Fig. 3. Symptom Checklist-90-Revised – change between baseline and day 42 by underlying disease (full analysis set; negative values denote improvement, PSD: post-traumatic stress disorder).

Safety/tolerability

25 of 50 patients reported 37 adverse events during 1848 days of treatment, corresponding to a frequency of 0.02 events per day. For 21 adverse events from 17 patients, a causal relationship to Silexan was not excluded. Most of these potentially attributable events were gastrointestinal disorders, notably eructation.

10 out of the 21 potentially attributable adverse events were mild and 11 were moderate in intensity. One serious adverse event (hospitalization for depression) occurred during the trial, but was assessed not to be related to the investigational treatment.

Means of safety laboratory measures and vital signs did indicate neither any systematic shifts nor any individually pathological values emerging during treatment with Silexan.

Discussion

To date clinical research into the efficacy of lavender preparations has been focused on the herb's anxiolytic properties, relaxation, sleep induction, and mood alleviation (Kasper et al. 2010). This is the first published trial to investigate the effects of the herbal drug in subthreshold anxiety in relation to neurasthenia and PSD. Data to compare with those of our trial is thus unavailable. On the other hand, a large number of clinical trials have been performed for synthetic drugs, particularly in PSD (Asnis et al. 2004), but they have used different outcome measures and endpoints. Therefore, interpretation of the effect sizes in this study has to rely on clinical judgment as well as on comparison to data obtained in the context of standardization of the psychiatric scales that were used as outcome measures.

Compared to reference values of SCL-90-R, D-S and STAI for healthy individuals and for patients suffering from neurotic conditions (Weyer 2004), the participants of this exploratory trial represent a sample of patients whose profiles were characterized by elevated values on various subscales, notably obsessive-compulsive thinking and behavior, interpersonal sensitivity, restlessness, anger and hostility, paranoid ideation, anxiety and depression, as well as disturbed sleep. After 6 weeks of open-label treatment, the mentioned properties of Silexan led to significant and clinically meaningful improvements as compared to baseline. Subscales with particularly large improvements were depressed mood, obsessive-compulsive perceptions, paranoid thinking, as well as self-perceived physical and psychic impairment in general, sleep efficiency, and waking-up frequency and duration. During standardization of the German version of the SCL-90-R Franke (1995) has obtained a mean value of 0.33 for the Global Severity Index (GSI) in a population of healthy adults, whereas Wuchner and Eckert (1993) have reported a mean value of 1.29 for a sample of patients with neurotic disturbances. Compared to these results the post-treatment GSI scores of the patients in our trial were mainly in the lower abnormal range.

In addition to the improvements observed in the SCL-90-R, the study participants also exhibited an amelioration of anxiety levels. Furthermore, a main area of improvement was patients' self-perception of mental health impairments and their impact on aspects of daily living and quality of life (SF-36).

Reduced Personal Accomplishment and the Depersonalization subscales of the MBI showed only negligible changes between baseline and treatment end. This might be explainable by the fact that patients primarily suffering from burnout syndrome were not included. Nevertheless we had chosen to administer the MBI to obtain a broader picture of possible clinical effects of Silexan. A relevant treatment effect was indeed observed for the Emotional Exhaustion subscale which covers symptoms relevant in both neurasthenia and PSD. However, we feel that the additional information contributed by the MBI was rather limited.

Systematic differences in effect between neurasthenia and PSD or the combination of both, i.e. disease specific patterns of improvement, were not easily detectable, and the few larger differences that emerged (e.g. more pronounced increase in sleep efficiency in patients with neurasthenia as compared to PSD; larger relative reduction of the D-S depression score in patients with PSD as compared to neurasthenia alone) could be attributable to chance or to baseline differences as well as to a systematic effect. Due to the small sample sizes within the subsets of patients defined by the underlying disease such observations call for an independent replication.

Sedation, fatigue and 'typical SSRI side effects' like gastrointestinal disturbances, agitation or insomnia (Masand and Gupta 2003; Preskorn 1995; Starcevic 2005; Trindade et al. 1998) as well as phenomena like weight gain and sexual dysfunction (Fava et al. 2000; Hirschfeld and Vornik 2004; Nelson et al. 2006) are side effects that are not uncommon even with newer-generation drugs. These reactions may seriously interfere with essential activities of daily living (e.g. with the ability to operate machinery or to drive a vehicle) and may thus adversely affect the patients' quality of life. In this trial, the most frequently reported adverse event potentially related to Silexan was eructation that has been reported with Silexan before (Woelk and Schlaefke 2010) as in trials with other ethereal oils, e.g. peppermint oil (Liu et al. 1997). None of the potentially attributable adverse events were severe or had any serious impact on social or vocational activities. Silexan showed no unwanted sedative effects and no signs of tachyphylaxis. It has no potential for drug abuse.

In a double-blind controlled trial performed by Kasper et al. in patients with anxiety disorder (Kasper et al. 2010), the incidence of adverse events during treatment with Silexan was comparable to placebo with no specific adverse reactions, altogether somewhat lower than in our trial. That may be due to the open label character of our trial.

Limitations as to judge efficacy are clearly given by the same, esp. as neurotic complaints are prone to improve by contextual factors. However, this trial may open perspectives for further investigation into Silexan.

Conclusion

After 6 weeks with 1×80 mg/day Silexan, patients suffering from neurasthenia or post-traumatic stress disorder showed statistically significant and clinically meaningful improvements of concomitant symptoms like restlessness, sleep disturbances, and sub-threshold anxiety affecting their general mental health status and quality of life. The investigation did not reveal any previously unknown risks associated with the intake of the herbal medicinal product. Therefore further investigation with Silexan in neurasthenia and PSD appears to be justified and promising.

Conflict of interest

The Department for Natural Healing, Charite University Medicine Berlin, has received research grants from Dr. Willmar Schwabe GmbH & Co. KG, manufacturer of Silexan. SS (Schaper) and BU had been employed by these research grants during the study.

AD and SS are employees of Dr. Willmar Schwabe GmbH & Co. KG, manufacturer of Silexan.

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