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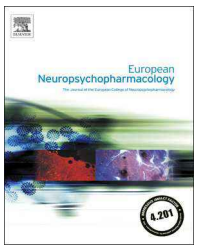

Efficacy of orally administered Silexan in patients with anxiety-related restlessness and disturbed sleep - A randomized, placebo-controlled trial

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Clinical trial;
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Abstract
The anxiolytic effect of Silexan, a patented active substance with an essential oil produced from *Lavandula angustifolia* flowers, was investigated in patients with anxiety-related restlessness and disturbed sleep. 170 out-patients with a diagnosis of restlessness (ICD-10 R45.1), a Hamilton Anxiety Scale (HAMA) total score ≥ 18 points and ≥ 2 points for HAMA items 'Tension' and 'Insomnia' participated in this randomized, double-blind trial and received 80 mg Silexan or placebo once daily for 10 weeks. Patients with clinically important other psychiatric or neurological disorders potentially interfering with the assessment of treatment efficacy were excluded. Outcome variables were the HAMA as well as the Pittsburgh Sleep Quality Index (PSQI), the Zung Self-rating Anxiety Scale, a State Check inventory and the Clinical Global Impressions questionnaire. In the Silexan group the HAMA total score decreased from an average of 25.5 ± 6.0 points at baseline to 13.7 ± 7.0 points at treatment end, compared to a decrease from 26.5 ± 6.1 to 16.9 ± 9.8 for placebo, corresponding to decreases of 12.0 and 9.3 points (marginal means), respectively (group difference: $p=0.03$, ANCOVA with factor treatment and baseline value as covariate). In all outcome measures the treatment effect of Silexan was more pronounced than with placebo. According to the HAMA, 48.8% and 33.3% of the patients were responders (Silexan, placebo; reduction $\geq 50\%$; $p=0.04$) and 31.4% and 22.6% achieved remission (HAMA <10; $p=0.20$). 33.7% (Silexan) and 35.7% (placebo) of the participants reported adverse events. The study confirms the calming and anxiolytic efficacy of Silexan.

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1. Introduction

Restlessness and disturbed sleep both belong to the symptom spectrum of anxiety disorders (American Psychiatric Association, 2013; World Health Organization, 1992) although both may also appear as symptoms of other psychiatric or somatic conditions or even as independent diagnostic categories. Under the current diagnostic systems patients who present with restlessness and/or disturbed sleep related to anxiety, but who do not meet all diagnostic criteria of generalized anxiety disorder (GAD), may be diagnosed to suffer from unspecified anxiety disorder (ICD-10 F41.9) or other specified anxiety disorder (DSM-5 300.09) if anxiety is perceived as the predominant factor of the clinical picture (Lawrence and Brown, 2009). Such a condition may be regarded as a subthreshold variation of GAD when some, but not all of its criteria, are met (Volz et al., 2011). If, however, restlessness rather than anxious mood is perceived as the prominent symptom, a patient may instead be diagnosed to be suffering from restlessness and agitation (ICD-10 R45.1). In a primary care setting, where subthreshold anxiety disorders and their comorbidity symptoms are particularly common (Wittchen et al., 2002), a differentiation between anxiety disorder and restlessness and agitation disorder may not always be easily achieved.

Recently completed randomized, controlled clinical trials have demonstrated that Silexan[‡] is a potent anxiolytic drug with proven efficacy in generalized anxiety disorder (GAD; Kasper et al., 2014) as well as in subthreshold anxiety (Kasper et al., 2010b). In contrast to initial speculations that the anxiolytic action of lavender oil is caused by a benzodiazepine-like effect on the $GABA_A$ receptors (Huang et al., 2008) a recent study performed by Schuwald et al. (2013) did not identify any interaction of Silexan to known targets of other anxiolytic drugs such as the $GABA_A$-receptor, norepinephrine, serotonin, or dopamine transporters, or monoamine-oxidase-A (MAO-A). Instead, Silexan caused a potent inhibition of voltage dependent calcium channels (VOCCs) in synaptosomes, primary hippocampal neurons and stably over-expressing cell lines comparable to pregabalin. In contrast to pregabalin, however, Silexan did not bind to the gabapentin binding site at the $\alpha_2\delta$-1 and -2 subunits of the presynaptic VOCCs of the P/Q-type and is supposed to bind to a different target structure that has not yet been identified. Anxiety disorders have been pathophysiologically linked to an over-reaching, situationally inadequate stress response of the central nervous system and of the hippocampus in particular (Satpute et al., 2012) where the inhibition by Silexan was shown to be mainly mediated via N-type and P/Q-type VOCCs. In another recent study in healthy volunteers, Baldinger et al. (2014) showed that Silexan significantly reduces the serotonin-1A receptor (5-HT1A) binding potential in the brain clusters encompassing the temporal gyrus, the fusiform gyrus, the hippocampus, the insula and the anterior cingulate cortex. These mechanisms may explain the anxiolytic effect of the drug.

Among the symptoms of anxiety disorders, the inability to relax, the feeling of constantly being restless or 'on edge', is perceived to be particularly agonizing by many patients. A calming, yet not sedating effect, is therefore considered to be of major importance in the drug treatment of anxiety. This report presents the results of a randomized, placebo-controlled clinical trial that was performed to investigate the efficacy and tolerability of Silexan in patients suffering from restlessness and disturbed sleep in the context of subthreshold anxiety disorder.

[‡]Silexan® is the herbal active substance of the medicinal product LASEA® (Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany).

2. Experimental procedures

2.1. Objectives, design overview, ethical conduct

In the study two questions were investigated. One objective was to confirm the efficacy of Silexan in reducing the participants' anxiety levels by demonstrating superiority over placebo. The other objective was to show the efficacy of Silexan in improving sleep. In this paper we focus on the anxiolytic effect of the drug.

The study was a double-blind, randomized, multicenter trial with 2 parallel groups (EudraCT: 2004-003975-35). A single-blind screening and washout phase of 3–7 days' duration, during which all participants received placebo, was followed by 10 weeks double-blind treatment with Silexan or placebo according to random assignment. Post-baseline efficacy and safety assessments were performed every 2 weeks.

The study protocol was reviewed and approved by an independent ethics committee. All patients provided written informed consent. The principles of Good Clinical Practice and the Declaration of Helsinki were adhered to.

2.2. Participants

The clinical part of the trial was performed between June 2005 and June 2006 in 17 general and psychiatric practices in Germany. Male and female patients of any ethnic group and between 18 and 65 years of age were asked for their participation if they suffered from restlessness and agitation according to the criteria of ICD-10 diagnostic category R45.1 (World Health Organization, 1992). The diagnosis was established by the investigators of the centers personally and had to be supported by a score of at least 5 points on an observer rated 10-point visual analog scale determining the extent of restlessness and agitation as well as by substantial, disease related impairment of essential activities of daily living. Moreover, eligible participants had to present with a total score ≥ 18 points on the Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1976) and with minimum scores of 2 points for HAMA items 'Tension' and 'Insomnia'. Disturbed sleep was confirmed by a total score ≥ 6 points on the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). These criteria were required to be met at both study inclusion and baseline.

Patients with a HAMA total score decrease $\geq 25\%$ between study inclusion and baseline were not randomized. Moreover, any clinically important psychiatric or neurological diagnosis within 6 months before the study except anxiety disorders, mild or moderate depression, somatoform disorders, neurasthenia, personality disorders or primary insomnia led to exclusion. Patients assessed to be suicidal, or those with substance abuse disorder, were also excluded. Other psychotropic medication or muscle relaxants as well as psychotherapy were not allowed during study participation (in case of previous medication an appropriate wash-out period had to be observed).

2.3. Interventions, blinding

Silexan is a patented active substance with an essential oil produced from *Lavandula angustifolia* flowers by steam distillation and complies with the monograph Lavender oil of the Ph.Eur. It exceeds the quality definition of the Ph.Eur. with respect to items important for efficacy and tolerability. Batch to batch consistency is assured by well defined, highly standardized processes of

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manufacture. Immediate release soft gelatin capsules containing 80 mg of Silexan or identically matched placebo capsules were used. The smell of the study drugs was matched by flavoring the placebo capsules with 1/1000 of the amount of lavender oil contained in the Silexan capsules. Randomized patients administered 80 mg (one capsule) per day in accordance with the monograph on lavender flowers issued by the German federal health authority (Bundesgesundheitsamt, 1984) and with the marketing authorization of the product. The study participants were instructed to swallow the capsules unchewed.

During the 3–7 days screening period all participants took one capsule of placebo single-blind, once daily in the morning. During double-blind treatment eligible patients administered one capsule of Silexan or placebo per day for a scheduled period of 10 weeks.

2.4. Measures of efficacy and safety

HAMA (observer-rating) absolute total score change between baseline (i.e. start of randomized treatment) and the final examination at week 10 was pre-defined as the primary outcome measure of treatment efficacy regarding the anxiolytic effect of Silexan. PSQI (self-rating) absolute total score change between baseline and the final examination at week 10 was the primary outcome measure with respect to the improvement of sleep. Both rating scales were conducted during each scheduled visit. In a supplementary responder analysis participants with a HAMA total score decrease by at least 50% of the baseline value between baseline and end of treatment were defined to be responders, and those who showed a decrease to a HAMA total score <10 points at treatment end were classified as remitters. Further efficacy outcome measures also included HAMA subscores, the Zung Self-rating Anxiety Scale (SAS; Zung, 1971), the Clinical Global Impressions observer rating scale (CGI; National Institute of Mental Health, 1970), and the State Check (SC) scale, a self-designed two-item inventory globally assessing the extent of restlessness and of impairment of sleep on a 4-point verbal rating scale which included the choices 'never/seldom', 'sometimes', 'often', and 'mostly/always'. Safety and tolerability were assessed based on adverse events (AEs) reported spontaneously as well as on physical and ECG examinations, vital signs, and routine laboratory measurements.

2.5. Random sequence generation, allocation concealment, implementation

The random code was generated by a qualified person in the sponsor's biostatistical department otherwise not involved in the trial, using a validated computer program (RCODE, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany). Randomization was performed in fixed-size blocks at a ratio of 1:1 with stratification by trial center. The study drugs were dispensed to the centers in numbered containers. The investigators were instructed to assign the lowest available random number after confirming a patient's eligibility for randomized treatment. The random block size was withheld from the investigators until completion of the trial in order to reduce the predictability of the randomization.

2.6. Statistical methods, sample size

Multiple testing was performed by applying a closed testing procedure (Lehmacher et al., 1991). As global null hypothesis lack of superiority of Silexan over placebo either with regard to HAMA or PSQI total score change from baseline was tested using O'Brien's Ordinary Least Squares (OLS) procedure (O'Brien, 1984). In another step each of these outcome measures was to be tested separately using independent samples t-tests and applying the same experimentwise type I error level of $\alpha=0.025$ (one-sided) for each test. The study was planned and performed with an adaptive interim analysis (Bauer and Köhne, 1994) with options for sample size reassessment and hypothesis testing. At the interim stage a local type I error level of $\alpha_1=0.152$ and an upper bound of $\alpha_0=0.20$ for stopping for futility applied. This report presents the results of the interim analysis after which it was decided to terminate the study.

In accordance with recent European guidance (Committee for Medicinal Products for Human Use, 2013) a baseline adjustment of the treatment effects was performed for HAMA total score change using an analysis of covariance model (ANCOVA) with treatment as a factor and the baseline value as a covariate. Marginal means were estimated to describe the anxiolytic treatment effect.

The primary analysis population for confirmatory testing was the full analysis set (FAS) which included all patients who had received the randomized treatment at least once and who had at least one post baseline outcome assessment for both primary outcome measures. Missing values were replaced by carrying the last observation forward (LOCF). An additional per protocol (PP) analysis was performed as a sensitivity analysis. All decisions regarding patient eligibility for the different analysis data sets were obtained before code breaking. Secondary efficacy and safety measures were analyzed descriptively. All p-values are two-sided unless otherwise noted; two-sided p-values ≤ 0.05 are considered descriptively significant. The results presented below apply to the FAS unless otherwise noted.

Based on results from previous research the sample size calculation was tailored to detect a treatment group mean value difference of 3 points assuming a standard deviation (SD) of 6 points for HAMA total score change and a mean value difference of 1.5 points with an expected SD of 3 points for PSQI total score change. Under these assumptions at least 2×78 patients were required in the FAS to achieve a power of 80% for testing the single null-hypotheses each with a one-sided t-test using Bonferroni adjusted type I error rates of $\frac{\alpha}{2}=0.0125$. Since HAMA and PSQI total score change were assumed to be correlated, it was expected that the application of the OLS closed testing procedure would lead to an increase in power as compared to the conservative Bonferroni procedure.

3. Results

3.1. Recruitment, participant flow

A total of 179 patients were included and assessed for eligibility, and 170 were randomized (Silexan 86; placebo 84). Reasons for non-randomization, premature termination or exclusion from the PP analysis are shown in Figure 1. All randomized patients were analyzed for efficacy (FAS) and safety. In the Silexan group 12 patients (14.0%) and 10 in the placebo group (11.9%) terminated randomized treatment before the scheduled end. Six (Silexan) and 4 (placebo) of these early terminators in whom withdrawal from the trial was neither related to lack of efficacy nor to a potentially related AE were excluded from the PP analysis whereas those withdrawn for potential lack of efficacy or tolerability were included.

3.2. Baseline data

Both treatment groups' baseline demographic and efficacy outcome measures were comparable, with a slight tendency to higher values of the efficacy outcomes in the placebo group (indicating slightly more severe impairment) (Table 1). One patient in the placebo group was Asian while all other participants were Caucasian. More than half of the patients in both groups were assessed to be markedly or severely ill. According to the SC inventory 86.0% of the patients in the Silexan group and 90.5% in the placebo group

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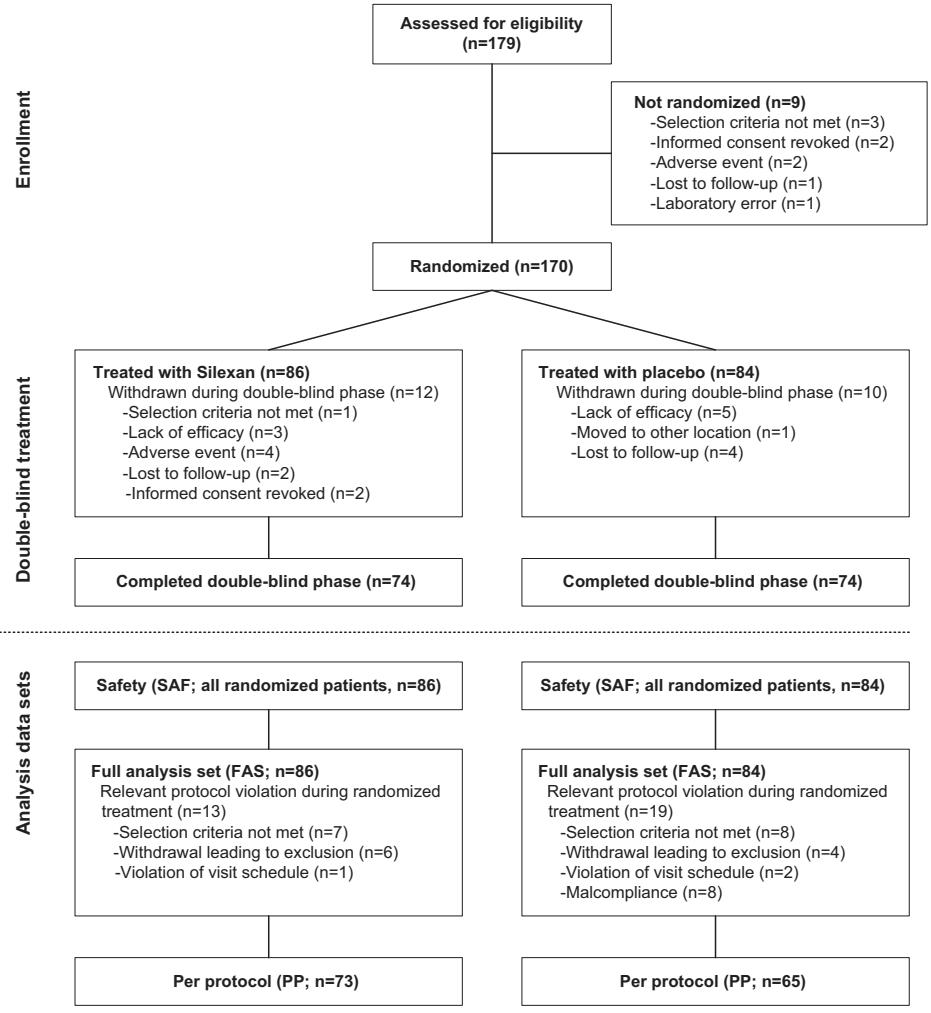

Figure 1 Disposition of patients, analysis data sets.

felt often or always restless, and all participants in both groups were often or always tired. No systematic treatment group differences were observed for medical history and for previous and concomitant medication (data not shown).

3.3. Treatment compliance

Compliance was assessed by comparing the number of unused capsules returned by the patients to the expected number assuming a fully protocol compliant intake. Average study medication intake was 100.7%±2.8% (mean±SD) of the prescribed amount for Silexan and 100.3%±4.1% for placebo, with interquartile ranges of 100.0–101.5% and 98.6–101.4% for Silexan and placebo, respectively. Compliance was considered acceptable in case of an administered amount within a range of 80-120% of the prescribed amount for every 2-week period between the scheduled visits during randomized treatment. Eight patients (9.5%) in the placebo group (but none in the Silexan group) had to be excluded from the PP analysis due to lack of compliance (Figure 1). Moreover, minor compliance issues not leading to an exclusion were observed in 18 patients in the Silexan group (20.9%) and in 19 (22.6%) in the placebo group.

3.4. Efficacy

In the Silexan group the HAMA total score (primary outcome measure for anxiolytic efficacy) decreased from an average of 25.5±6.0 points (mean±SD) at baseline to 13.7±7.0 points at treatment end, compared to a decrease from 26.5±6.1 to 16.9±9.8 points in the placebo group (Figure 2), corresponding to decreases from baseline of 12.0 and 9.3 points, respectively (marginal means; Table 2). Between weeks 4 and 10 Silexan showed a statistically significant advantage over placebo with treatment group mean value differences ranging between 2.7 and 2.9 points in the FAS. In the corresponding PP analysis the treatment group mean value differences were even more pronounced, ranging between 3.5 and 3.8 points at Week 4 and thereafter. Subgroup analyses revealed that the treatment group difference favoring Silexan for HAMA total score change was more pronounced in patients with more severe baseline impairment. For example, the treatment group difference was 4.6 points (*t*-test: $p=0.03$) in patients with a baseline HAMA total score ≥ 26 points (median at baseline; Figure 3) and 4.9 points ($p=0.01$) in patients with a score of more than 7 points (median) on the 10-point restlessness and agitation visual analog scale completed at baseline to support the diagnosis of restlessness and agitation.

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Table 1 Demographic and other baseline data (full analysis set; absolute frequency (%), mean ± SD, or median and range (age only)).

	Silexan (n=86)	Placebo (n=84)	p[a](two-sided)
Sex			
Female	62 (72.1%)	60 (71.4%)	0.92[a]
Male	24 (27.9%)	24 (28.6%)	
Age (years)	49 (22-67)	48 (21-67)	0.57[c]
Body mass index (kg/m^2)	25.8 ± 4.6	26.0 ± 5.1	0.79[c]
HAMA	25.5 ± 6.0	26.5 ± 6.1	0.27[c]
PSQI	12.2 ± 2.5	12.7 ± 2.8	0.19[c]
Zung SAS	54.5 ± 12.3	55.9 ± 10.3	0.43[c]
CGI Item 1: markedly or severely ill	49 (57.0%)	46 (54.8%)	0.51[b]

HAMA, Hamilton Anxiety Rating Scale; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-rating Anxiety Scale; CGI, Clinical Global Impressions scale.
[a]Pearson χ^2-test.
[b]Mantel-Haenszel χ^2-test for original (uncategorized) distribution.
[c]t-Test.

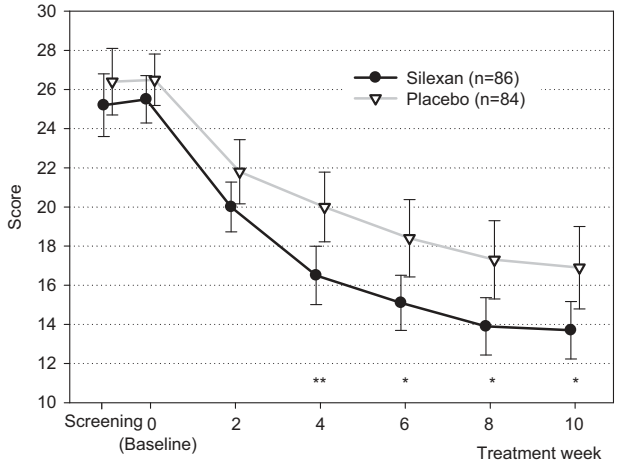

Figure 2 Hamilton Anxiety Scale total score time course (means and 95% confidence intervals, full analysis set, last observation carried forward. t-Test for treatment group difference regarding change from baseline: $^*p \leq 0.05$; $^{**}p \leq 0.01$, two-sided).

In the FAS the global null hypothesis predicting no superiority of Silexan over placebo either with regard to HAMA or PSQI total score change from baseline could not be rejected (p=0.091; PP analysis: p=0.025; one-sided p-values). This was mainly attributable to a small treatment effect with respect to PSQI total score change.

In the Silexan group, 48.8% of the patients treated with Silexan and 33.3% of those in the placebo group showed a HAMA total score decrease by at least 50% compared to baseline and were classified as responders (treatment group difference: p=0.04, χ^2-test). The percentages of patients with a HAMA total score <10 points at treatment end, who were thus classified as having achieved remission, were 31.4% and 22.6% for Silexan and placebo, respectively (p=0.20; Figure 4).

The self-rated SAS showed a decrease in anxiety symptoms by averages of 11.2 ± 10.1 points for Silexan and 9.3 ± 10.4 points for placebo. The results for the restlessness scale of the SC inventory obtained at treatment end (week 10) are presented in Figure 5. Compared to baseline, the percentage of patients who felt never, seldom, or sometimes restless (as opposed to often mostly, or always) increased from 14.0% at baseline to 71.4% in the Silexan group and from 9.5% to 57.8% in the placebo group, with a significant advantage for Silexan (p=0.01). Of note, the number of patients assigned to the most favorable category of the scale, 'never/seldom', increased from 1 (1.2%) at baseline to 18 (20.9%) for Silexan and from 0 to 7 (8.3%) in the placebo group whereas the patient numbers in the least favorable category, 'mostly/always', decreased from 30 (34.9%) to 4 (4.7%) and from 29 (34.5%) to 9 (10.7%) for Silexan and placebo, respectively.

Moreover, 46 (54.8%) of the patients treated with the herbal essential oil never, seldom, or sometimes suffered from disturbed sleep according to the SC inventory assessment at week 10, compared to 37 (44.6%) in the placebo group. In the CGI assessment at week 10, 17 participants in the Silexan group (19.8%) were only borderline ill or not at all ill, and 45 (52.3%) showed moderate or marked improvements from baseline, compared to 12 (14.3%) and 27 patients (32.2%) in the placebo group, respectively.

3.5. Safety/tolerability

During and up to 7 days after the end of randomized treatment 34 AEs were reported by 29 (33.7%) patients exposed to Silexan compared to 36 events reported by 30 patients (35.7%) in the placebo group, corresponding to one AE in 181 days of exposure to Silexan and to one event in 171 days of placebo treatment. In the Silexan group 11 of the 34 AEs were observed during the first 2 weeks of randomized treatment. Adverse events occurring in at least 3 patients in one treatment group were influenza (Silexan 1, 1.2%, placebo 5, 6.0%), eructation (Silexan 6, 7.0%, placebo 0), and bronchitis (Silexan 3, 3.5%, placebo 3, 3.6%).

Nine patients in the Silexan group (10.5%) and 4 in the placebo group (4.8%) had one AE in which a causal relationship to study medication could not be excluded during double-blind assessment. All potentially related events in

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Table 2 Hamilton Anxiety Scale total score – change between baseline and subsequent visits (last observation carried forward; marginal means, mean value difference with 95% confidence interval, and *p*-value for treatment effect determined by analysis of covariance with baseline value as covariate).

	Marginal means		Mean value difference, 95% confidence interval		*p*
	Silexan	Placebo			
Full analysis set					
N	86	84			
Week 2	−5.6	−4.6	−1.0	[−2.77;0.71]	0.24
Week 4	−9.2	−6.3	−2.9	[−4.90; −0.86]	0.01
Week 6	−10.6	−7.9	−2.7	[−4.85; −0.48]	0.02
Week 8	−11.8	−9.0	−2.8	[−5.06; −0.52]	0.02
Week 10	−12.0	−9.3	−2.7	[−5.02; −0.28]	0.03
Per protocol					
N	73	65			
Week 2	−5.5	−4.1	−1.4	[−3.22; −0.46]	0.14
Week 4	−9.2	−5.7	−3.5	[−5.62; −1.35]	<0.01
Week 6	−10.7	−7.2	−3.6	[−5.98; −1.16]	<0.01
Week 8	−12.1	−8.3	−3.8	[−6.33; −1.33]	<0.01
Week 10	−12.5	−9.0	−3.5	[−6.03; −0.95]	0.01

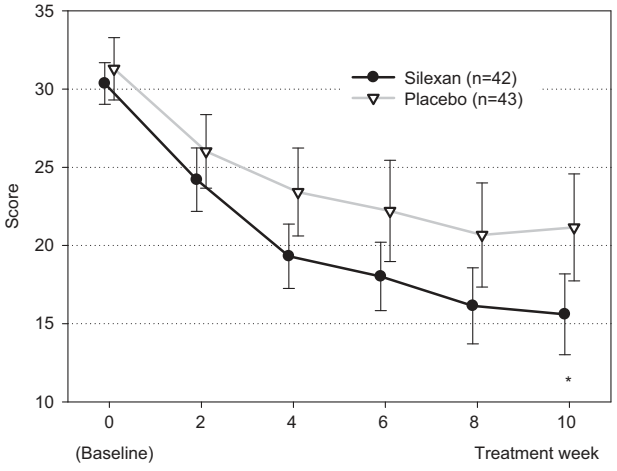

Figure 3 Hamilton Anxiety Scale (HAMA) total score time course - subset of patients with HAMA baseline total score ≥ 26 points (means and 95% confidence intervals, full analysis set, last observation carried forward. *t*-Test for treatment group difference regarding change from baseline: $^*p \leq 0.05$, two-sided).

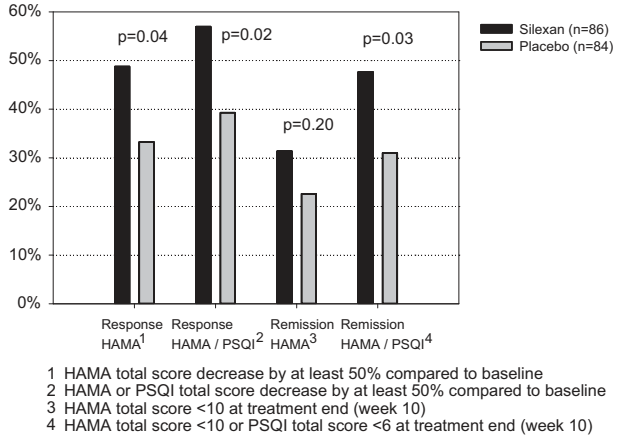

Figure 4 Response and remission based on different HAMA and PSQI criteria (percent of patients, χ^2-test *p*-values; full analysis set).

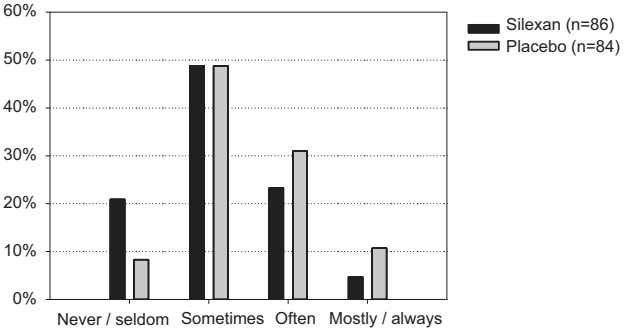

Figure 5 State Check inventory, 'Restlessness' scale – ratings at week 10 (percent of patients, χ^2-test *p*-value=0.005; full analysis set).

the Silexan group belonged to the system organ class of gastrointestinal disorders (eructation 6, 7.0%; diarrhea, gastritis, oral discomfort 1, 1.2%).

No serious events were observed.

4. Discussion

Restlessness and disturbed sleep are among the main indications of traditional medicinal use of lavender (British Herbal Medicine Association, 1996; Chu and Kemper, 2001). It is therefore not surprising that both indications are supported by a monograph issued by the German Federal Health Agency already in 1978 which approved the medicinal use of preparations from lavender flowers (Bundesgesundheitsamt, 1984). However, recent research on the efficacy and tolerability of Silexan, currently the only lavender oil preparation

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with pharmaceutical grade (Ph.Eur.) used as oral medicinal product, has focused on the potential of the drug as an anxiolytic and has demonstrated that it has a significant and clinically meaningful anxiolytic effect in both syndromal and subthreshold anxiety disorder (Kasper, 2013; Kasper et al., 2014, 2010b). This study was performed to assess the effect of Silexan in patients who also suffer from anxiety but whose prominent symptoms are restlessness and disturbed sleep.

The study shows a significant beneficial effect of Silexan on restlessness, which was not investigated for the drug as an outcome in its own right previously. Compared to placebo the reduction of restlessness in patients treated with the herbal essential oil was particularly pronounced in those who had felt restless always or most of the time at baseline.

The anxiolytic effect of Silexan already observed during previous research was confirmed. An advantage over placebo was clinically detectable already after 2 weeks of randomized treatment, became statistically significant after 4 weeks and remained so until the end of the 10-week treatment period. The magnitude of the treatment effect for HAMA total score decrease after 10 weeks observed in this study was in the range of the effect reported by Kasper et al. (2014) for Silexan 80 mg/d in patients with GAD and slightly lower than in a previous trial in subthreshold anxiety disorder (Kasper et al., 2010b). The clinical importance of these results is underlined by significant advantages of Silexan regarding responder and remission rates the criteria of which were pre-specified according to scientifically well-established definitions (e.g., Bandelow, 2006). It is also important to note in this context that the magnitude of the treatment effect in this trial was particularly large in patients who exhibited a comparatively high symptom load for restlessness and anxiety at baseline. This is consistent with the observation that in more severely impaired patients, as compared to patients with milder symptoms, the 'general' treatment effect brought on by the therapeutic alliance between the patient and the physician, which can be assumed to be present in any treatment including placebo, may become less important than the pharmacological effect of an 'active' drug.

The PSQI results do not indicate that Silexan had any sedative effects. This observation is supported by the fact that no adverse events indicating sedation were reported by patients treated with Silexan. The results are also consistent with those of other trials with Silexan during which no sedative effects were observed either (Kasper, 2013).

Sedating side effects have been described for many of the drugs currently recommended as first-line treatments of anxiety disorders, including selective serotonin reuptake inhibitors, benzodiazepines, and the antihistamine hydroxyzine (Bandelow et al., 2012). While Silexan has been shown to exert a pronounced anxiolytic effect that is in the range of synthetic drugs currently recommended for the pharmacological treatment of anxiety (Kasper et al., 2014, 2010a), clinical trials performed with the drug to date support the conclusion that Silexan has calming, anxiolytic, and sleep supporting properties without causing sedation. Patients may perceive this as an important contribution to their quality of life as unwanted sedative effects may cause significant limitations in their ability to pursue essential activities of daily living, e.g., to operate machinery or to drive a vehicle.

A limitation of the trial is that no formally validated psychiatric scale for assessing restlessness is currently available, and thus the authors had to use a self-developed scale which focused on the frequency at which the patient felt restless rather than on its intensity. While one-item measures tend to offer a lower reliability than multi-item scales, the advantage of the measure used in this study is that a high degree of content validity was achieved by asking the patients in a very straightforward manner how often they felt restless.

Another potential weakness of the trial is that the primary diagnosis for inclusion, ICD-10 R45.1, was based on the presence of symptoms of restlessness and agitation rather than on a psychiatric diagnosis. However, by requiring a (HAMA) total score ≥ 18 points for inclusion (with actually observed HAMA mean values around 26 points at baseline) we assured that these symptoms were related to clinically significant anxiety.

The constituents of herbal active substances in general are determined by the constituents of the medicinal plants from which they are produced, which are in turn affected by factors including genetic variation, environmental factors, and time and conditions of harvesting (Newall et al., 1996). Therefore batch-to-batch reproducibility may be an issue, and different products from the same plant may vary greatly in their composition and therefore not be used interchangingly (e.g., Wurglics et al., 2001). In case of Silexan, batch to batch consistency is assured by using a well-defined, highly standardized manufacturing process which also ascertains that the quality definition of the Ph.Eur. for lavender oil is met or exceeded with respect to items important for efficacy and tolerability.

In conclusion, Silexan had a pronounced calming and anxiolytic effect in patients suffering from restlessness associated with anxiety without causing sedation. Since the drug had a favorable effect on both aspects of the condition, it may be used with benefit to the patient irrespectively of whether the focus of the physician during the differential diagnosis lies on the aspect of restlessness or on anxiety. Silexan was very well tolerated.

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Contributors

Dr. Kasper was involved in the design of the original randomized clinical trial and contributed to the interpretation of the current analysis. Dr. Dienel helped to develop the design of the study. Dr. Kasper, Dr. Anghelescu and Dr. Dienel helped to draft the analysis plan of the current study and assisted in the creation of the initial draft of the manuscript. All authors contributed revisions to subsequent drafts of the manuscript, and have contributed to and approved the final manuscript.

Conflict of interest

Siegfried Kasper has received grant/research support from Eli Lilly, Lundbeck, Bristol- Myers Squibb, GlaxoSmithKline, Organon, Sepracor and Servier; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer, Organon, Schwabe, Sepracor, Servier, Janssen, and Novartis; and has served on speakers' bureaus for AstraZeneca, Eli Lily, Lundbeck, Schwabe (Spitzner), Sepracor, Servier, Pierre Fabre, and Janssen.

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Ion Anghelescu was a full-time employee at Janssen Pharmaceuticals from 2009 to 2012. He has served as a consultant or on advisory boards for Addex, Lundbeck, Otsuka, Janssen, Trommsdorf; and has served on speakers' bureaus for Janssen, Schwabe, Servier and Trommsdorf.

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