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ARTICLE

Lavender oil preparation Silexan is effective in generalized anxiety disorder – a randomized, double-blind comparison to placebo and paroxetine

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Abstract

The anxiolytic efficacy of the orally administered lavender oil preparation Silexan was investigated in generalized anxiety disorder (GAD) in comparison to placebo and paroxetine. In this randomized, double-blind, double-dummy trial 539 adults with GAD according to DSM-5 criteria and a Hamilton Anxiety Scale (HAMA) total score ⩾18 points participated and received 160 or 80 mg Silexan, 20 mg paroxetine, or placebo once daily for 10 wk. The primary efficacy endpoint was the HAMA total score reduction between baseline and treatment end. The HAMA total score decreased by 14.1±9.3 points for Silexan 160 mg/d, 12.8±8.7 points for Silexan 80 mg/d, 11.3±8.0 points for paroxetine, and 9.5±9.0 points for placebo (mean±S.D.). Silexan 160 and 80 mg/d were superior to placebo in reducing the HAMA total score ($p<0.01$) whereas paroxetine showed a trend towards significance ($p=0.10$) in the full analysis set. The difference between paroxetine and placebo was more pronounced in the analysis of observed cases (HAMA total score reduction: $p<0.01$). In the Silexan 160 mg/d group 73/121 patients (60.3%) showed a HAMA total score reduction ⩾50% of the baseline value and 56 (46.3%) had a total score <10 points at treatment end, compared to 70/135 (51.9%) and 45 (33.3%) for Silexan 80 mg/d, 57/132 (43.2%) and 45 (34.1%) for paroxetine, and 51/135 (37.8%) and 40 (29.6%) for placebo. In addition, Silexan showed a pronounced antidepressant effect and improved general mental health and health-related quality of life. Incidence densities of adverse events (AEs) were 0.006 AEs/d for Silexan 160 mg/d, 0.008 AEs/d for 80 mg/d, 0.011 AEs/d for paroxetine, and 0.008 AEs/d for placebo. In GAD Silexan is more efficacious than placebo. AE rates for Silexan were comparable to placebo and lower than for the active control paroxetine.

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Key words: Anxiety disorder, clinical trial, efficacy, lavender oil, Silexan.

Introduction

Anxiety disorders are by far the most prevalent psychiatric illness in Western Europe, with a 12-month prevalence of about 14% according to a recent survey (Wittchen et al., 2011). It has been estimated that about 22% of the patients in primary care who complain about symptoms of anxiety suffer from generalized anxiety disorder (GAD) (Wittchen, 2002). According to the current DSM 5 definition (American Psychiatric Association, 2013) which corresponds to the DSM-IV-TR definition (American Psychiatric Association, 2000) that applied when the trial was performed, GAD is defined by excessive anxiety and worry for at least 6 months, (a) that are difficult to control (b), and that are accompanied by at least three of six anxiety symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance) (c). The focus of anxiety and worry must not be confined to the symptoms of an Axis I disorder (d), they have to cause clinically significant distress or impairment in social, occupational or other important areas of functioning (e), and they must not be attributable to substance use or abuse (f). Surveys performed in different countries report lifetime prevalences of DSM-5 compliant GAD between 0.8 and 6.4% and 12-month prevalences between 0.5 and 3.7%

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(Grant et al., 2005). GAD is treated more often in general practices rather than by specialised psychiatrists (Wittchen et al., 2011).

The prevalence of GAD is about twice as high in women as in men, and it tends to increase with age (Somers et al., 2006; Merikangas et al., 2010). The condition is associated with a very high co-morbidity rate: in a survey reported by Carter and colleagues more than 90% of the patients with 12-month GAD also fulfilled the 12-month criteria for at least one other psychiatric disorder. Conditions with co-morbidity rates at or above 30% were major depression, dysthymia, social or specific phobia, and somatoform disorders (Carter et al., 2001). Nevertheless, GAD is perceived as an independent disorder rather than as a symptom or marker of another disorder (Grant et al., 2005).

According to the current disease management guidelines for anxiety disorders published by the World Federation of Societies of Biological Psychiatry (WFSBP; Bandelow et al., 2008), published clinical trials indicate strongest evidence of clinical efficacy in the treatment of GAD for selective serotonin reuptake inhibitors (SSRIs; notably escitalopram, paroxetine, and sertraline), serotonin–norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine), pregabalin (calcium channel modulator), and for quetiapine (second generation antipsychotic, SGA). Despite its proven anxiolytic efficacy imipramine (tricyclic antidepressant, TCA) was ranked as a secondary drug of choice, due to its unfavourable tolerability profile. Strong evidence for anxiolytic efficacy was also found for the benzodiazepines alprazolam, diazepam and lorazepam, which the WFSBP recommended mainly for treatment-resistant cases due to these drugs' addictive potential, and for the antihistamine hydroxyzine, for which strong sedating effects have to be considered. Other recent guidance documents (Canadian Psychiatric Association, 2006; Baldwin et al., 2011; National Collaborating Centre for Mental Health, 2011) are mainly consistent with the recommendations of the WFSBP; however, some also recommend the use of buspirone.

Although herbal medicines currently do not play an important role in the treatment of syndromal anxiety disorders, lavender essences have been known for centuries for their relaxing, calming and mood alleviating effects (Cavanagh and Wilkinson, 2002). In Germany a monograph issued by the Federal Health Agency in 1978 approved lavender flowers *(Lavandulae flos)* for the treatment of restlessness, insomnia, and nervous disorders of the intestines (Bundesgesundheitsamt, 1984). It is, therefore, not surprising that the potential use of the herb as an anxiolytic agent has become a focus of recent research (Kasper, 2013).

Whereas lavender products have mainly been used in aromatherapy or in balneotherapy, Silexan (an active substance manufactured by Dr Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany) is a novel, well-defined preparation from *Lavandula angustifolia* for oral use. The quality parameters of the essential oil are in full compliance with the monograph *Lavender oil* of the European Pharmacopoeia (European Directorate for the Quality of Medicines and Healthcare, 2005). In two double-blind, randomized trials in patients suffering from subsyndromal anxiety disorder (Kasper et al., 2010b) or from restlessness, agitation, and disturbed sleep (Kasper et al., 2010a) Silexan was superior to placebo on reducing the total score of the Hamilton Anxiety Scale (HAMA; Hamilton, 1976) during a treatment period of 10 wk. Another double-blind, randomized trial compared the anxiolytic effects of Silexan and lorazepam in patients with GAD. Both drugs were determined to be comparably efficacious regarding HAMA total score reduction during a treatment period of 6 wk (Woelk and Schläfke, 2010). In Germany Silexan is authorised as a medicinal product for the treatment of restlessness related to anxious mood, with a recommended dosage of 80 mg administered once daily.

Although the anxiolytic efficacy of Silexan has already been demonstrated, empirical data on the medically important indication of GAD are lacking. In order to investigate the effect of the herbal drug, we present the results of a study in which two different dosages of Silexan were compared to placebo and to paroxetine in patients suffering from GAD according to DSM-5 criteria. Paroxetine was chosen as an active comparator because its use is well established in GAD, and it is among the currently recommended pharmacological first-line treatments for the disorder.

Method

Protocol and design, objectives

This randomized, double-blind, double-dummy, multicentre trial with four parallel groups was planned and performed according to an adaptive two-stage design. The primary objective of the study was to demonstrate the superiority of Silexan over placebo in reducing the participants' HAMA total scores during randomized treatment. A secondary objective was to compare the anxiolytic efficacy of Silexan with that of paroxetine.

The study started with a treatment free screening and washout period of 3–7 d duration. Participants meeting the selection criteria were then randomized to 10 wk of double-blind treatment with one of two different dosages of Silexan, paroxetine, or placebo, with efficacy and safety assessments performed after 2, 4, 6, 8, and 10 wk. The treatment phase was followed by a 1 wk down-titration phase introduced for the withdrawal of paroxetine, and to document possible discontinuation effects.

The protocol was reviewed and approved by the independent ethics committee of the medical faculty of the University of Würzburg, Germany. All patients provided written informed consent. The principles of

good clinical practice and the Declaration of Helsinki were adhered to.

Participants

The study participants were male and female out-patients who were treated in 57 psychiatric and general practices in Germany. Participants had to be between 18 and 65 years of age and had to meet the diagnostic criteria for GAD according to DSM-IV-TR (300.02; corresponding to the criteria for GAD in DSM-5) and according to ICD-10 (F41.1). A HAMA total score $\geqslant$18 points was required for randomization, and, furthermore, eligible patients had to have scores of $\geqslant$2 points for HAMA items 1 ('anxious mood') and 2 ('tension'), a subscore $\leqslant$21 points for psychic anxiety as well as a Covi Anxiety Scale (CAS; Covi et al., 1981) total score $\geqslant$9 points. Main specific criteria for exclusion were the presence of another DSM-IV-TR Axis I diagnosis (including major depression) within 6 months before study entry, patients with predominant and/or severe depressive symptoms, risk of suicide, substance abuse, and schizophrenia. Other psychotropic medication and psychotherapy were not allowed during study participation, and psychotropic agents were also excluded during a 30 d period before the baseline visit.

Interventions, blinding

Silexan is a defined preparation from *Lavandula angustifolia* derived from the fresh flowering tops of the plant by steam distillation. The main constituents of the product are linalool and linalyl acetate, which account for about 70% of the ingredients. Batch to batch consistency is assured by well defined, highly standardized processes of cultivation, harvesting, and distillation. In this trial the product was available in immediate release soft gelatine capsules containing 80 or 160 mg of lavender oil. Paroxetine was supplied in capsules containing 20 mg. For each drug an identically matched placebo was available. The smell of the study drugs was matched by flavouring the placebo capsules with 1/1000 of the amount of lavender oil contained in the Silexan capsules, that is, 0.08 mg of Lavender oil per capsule of placebo. The study participants were instructed to swallow the capsules unchewed.

During double-blind, double-dummy treatment eligible participants took one capsule of Silexan/Silexan placebo and one capsule of paroxetine/paroxetine placebo per day according to the randomization. The therapeutic dosage for paroxetine was based on recommendations derived from individual dosing studies and analyses from the worldwide clinical database (Dunner and Dunbar, 1992) and corresponded to the marketing authorization of the drug in Germany where the trial was conducted. During down-titration all participants had to take the study medication every second day. In patients randomized to Silexan all capsules taken during down-titration contained placebo.

Outcomes

Efficacy and safety assessments were performed at baseline and at the end of weeks 2, 4, 6, 8, and 10. The primary efficacy outcome measure was the absolute decrease of the HAMA total score between baseline and week 10 or the individual end of treatment in case of premature withdrawal, the confirmatory analysis of which was performed in the full analysis set (FAS). Secondary efficacy outcome measures were response and remission which were defined as a HAMA total score decrease by at least 50% of the baseline value and as a HAMA total score <10 points, respectively, both of which were assessed at treatment end. Other secondary observer-rated efficacy outcome measures included the CAS, the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1967) and the Clinical Global Impressions (CGI; National Institute of Mental Health, 1970). Patient self-ratings were obtained using the Sheehan Disability Scale (SDS; Sheehan, 1983) and the SF-36 Health Survey Questionnaire (Ware and Sherbourne, 1992), which were administered at baseline and at the end of treatment only. The assessment of safety and tolerability was based on spontaneous reports of adverse events (AEs), physical examinations and routine laboratory measurements. Moreover, withdrawal symptoms were ascertained by administering the Physician Withdrawal Checklist (PWC-20; Rickels et al., 2008) at the end of randomized treatment as well as after the down-titration phase.

To assure uniform diagnostic and rating standards, all investigators were asked to participate in rater training before the beginning of patient inclusion.

Random sequence generation, allocation concealment, implementation

At baseline, eligible patients were randomized to Silexan 80 mg/d, Silexan 160 mg/d, paroxetine, or placebo at a ratio of 1:1:1:1. Fixed block randomization with stratification by trial centre was used; however, the investigators were not informed about the random block size until completion of the trial. A qualified person otherwise not involved in the trial generated the code using a validated computer program. The study drugs were dispensed to the centres in numbered containers. Upon inclusion into randomized treatment each patient received the lowest available number.

Statistical methods, sample size

The main objective of this trial was to demonstrate that Silexan 160 and 80 mg/d are superior to placebo in reducing the patients' anxiety levels expressed by the absolute change of the HAMA total score between baseline and

treatment end. Multiple confirmatory testing was accounted for by *a priori* ordering of hypotheses in the specified sequence (i.e. the confirmatory test for the comparison between the 80 mg/d dosage and placebo was to be performed only after the null hypothesis referring to the comparison between the 160 mg/d dosage and placebo had already been rejected) so that a type 1 error level adjustment was not required (Maurer et al., 1995). The study was performed according to an adaptive two-stage design, with one pre-planned interim analysis which included options for early stopping with rejection of the null hypothesis or for futility, or for sample size re-estimation in case of continuation (Kieser et al., 1999). A one-sided, studywise type 1 error rate of $\alpha=0.025$ was applied. In the interim analysis the local, one-sided type 1 error rate for rejection of the null hypotheses was $\alpha_1=0.0152$, and the futility boundary for finally accepting the null hypothesis was $\alpha_0=0.20$. Confirmatory testing was performed in the FAS using analysis of covariance (ANCOVA) models with treatment as a factor and HAMA total score at baseline as a covariate. In addition Cohen's d (Cohen, 1988) was calculated (using the pooled S.D. of both treatment groups in the denominator) to compare treatment effects of Silexan with other anxiolytic substances. No formal hypotheses were pre-specified to compare paroxetine and placebo as well as Silexan and paroxetine.

The FAS included all randomized patients who had at least one post-baseline assessment for the primary outcome measure. A per-protocol analysis data set (PPS) was chosen for sensitivity testing. Missing values were replaced by carrying forward the last observation. All secondary efficacy and safety measures, including efficacy comparisons between paroxetine and other treatments, were analysed descriptively. In order to assess the impact of drop outs on efficacy results, the subset of observed cases (OC) was evaluated for the FAS and the PPS. The subset of OC included only data from patients who did not discontinue prematurely and who were available for evaluation at the designated assessment visits. A special analysis data set was defined for the analysis of withdrawal symptoms using the PWS-20 scale: eligible patients had to have a minimum study medication period of 56 d and valid PWC-20 assessments at the end of randomized treatment as well as after the down-titration phase. Patients with relevant treatment non-compliance, as well as those with concomitant medication during down-titration which might have had an influence on withdrawal symptoms, were excluded.

The sample size was calculated assuming a clinically relevant difference of 3 points between Silexan and placebo for HAMA total score change *vs.* baseline and a common S.D. of 8 points for both Silexan 80 and 160 mg/d. Thus 130 patients per group were required to achieve a power of 80% for rejecting the null hypothesis already in the interim analysis using a local type 1 error rate of $\alpha_1=0.0152$ (one-sided) based on a *t*-test model. It was further assumed that the planned ANCOVA models would be at least as powerful as *t*-tests.

Results

Since the anxiolytic efficacy of Silexan could already be demonstrated in the interim analysis and the study was thus terminated according to the pre-specified stopping rules without performing a second part, this section reports the results of the interim analysis, which was thus also the final analysis for the trial.

Recruitment, participant flow

Between May 2007 and November 2010, 616 patients were included in 57 general and psychiatric practices in Germany, 539 patients were randomized and 536 (Silexan 160 mg/d 128; 80 mg/d: 135; paroxetine: 137; placebo: 136) were treated. Reasons for non-randomization, premature termination or exclusion from the analysis data sets are shown in Fig. 1.

All treated patients were analysed for safety. Patients were analysed for efficacy in the FAS if they had been randomized and treated and provided any post-baseline efficacy data (baseline efficacy data were not carried forward). All decisions regarding patient eligibility were made before code breaking.

Baseline data

Across all treatment groups close to three quarters of the study participants were female (Table 1). All patients except two were Caucasians, although no ethnic groups were excluded. At baseline between 60% and 74% of the patients in each group suffered from an ongoing concomitant disease, the most frequent of which were vascular disorders, musculoskeletal disorders, and metabolic and nutritional disorders. Upon inclusion into the trial the study participants had been suffering from GAD for an average of about 2.5 yr, with average durations of the current episode around 1 yr in all treatment groups.

Baseline measures of anxiety levels, global condition and general well-being are shown in Table 2. HAMA mean values were clearly above the lower limit of 18 points required for inclusion, and the mean values for CGI Item 1 indicated that the patients in all groups were on average moderately to markedly ill. The table also shows that the patients in the Silexan 160 mg/d group showed somewhat higher baseline levels of anxiety and less favourable self-ratings of their general condition and well-being than those in the other groups, which did, however, not translate into a less favourable global investigator rating of mental illness (CGI Item 1). In all other aspects investigated, Tables 1 and 2 show

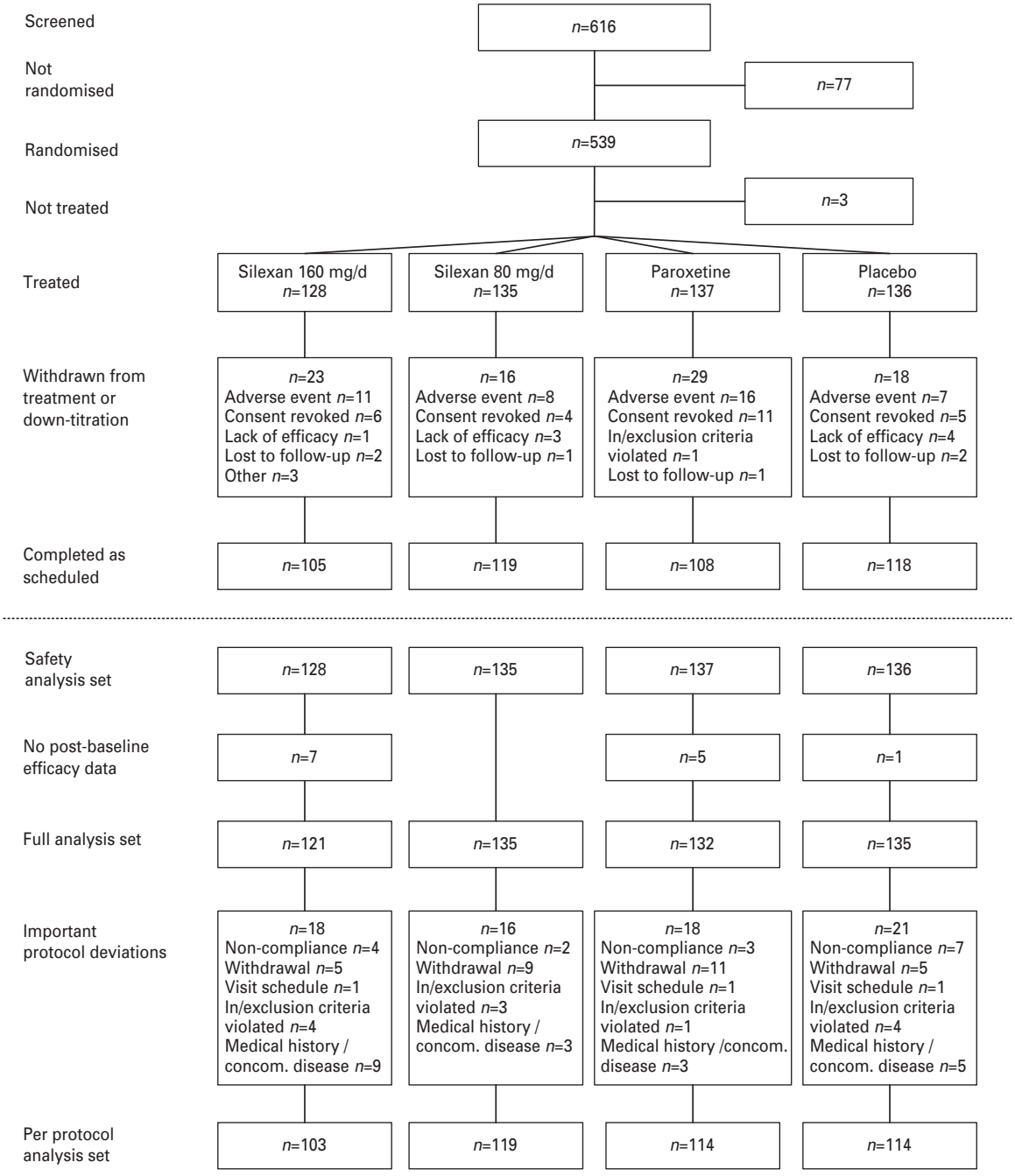

Fig. 1. Disposition of patients, analysis data sets.

that the four treatment groups were comparable at baseline.

Investigational treatment

Average treatment compliance (assessed by medication counting) within the four treatment groups ranged between 99.0 and 99.7%, with S.D. ranging between 3.1 and 4.3%. Study drug intake <80% or >120% of the prescribed amount was considered a major protocol violation. This is why between 1.5% (Silexan 80 mg/d; 2 of $n=135$) and 5.1% (placebo; 7 of $n=136$) of the treated patients were excluded from the PPS for non-compliance (Fig. 1).

Efficacy

During randomized treatment all study groups showed a monotonic decrease of the HAMA total score that was most pronounced in the Silexan treatment groups, followed by paroxetine and placebo (Fig. 2). In the FAS Silexan 160 mg/d was significantly superior to placebo after 4 wk of treatment (mean value difference to placebo: 2.6 points; $p<0.01$, 2 sided t test) as well as at all

Table 1. Demographic and clinical characteristics at baseline (Full Analysis Set; mean±S.D. or absolute frequency and %)

	Silexan 160 mg/d (n=121)	Silexan 80 mg/d (n=135)	Paroxetine (n=132)	Placebo (n=135)	p (2-sided)
Sex: female	89 (73.6%)	95 (70.4%)	102 (77.3%)	99 (73.3%)	0.65[a]
Age (yr)	47.1±11.8	45.7±11.5	45.8±12.4	44.6±12.3	0.52[b]
Time since first diagnosis of GAD (yr)	2.8±5.3	2.3±5.0	2.3±4.1	2.6±4.7	0.39[b]
Duration of current episode (yr)	1.1±1.5	1.0±1.1	1.0±1.8	1.1±1.4	0.91[b]

[a] χ^2 test.
[b] Kruskal–Wallis test.
GAD, generalized anxiety disorder.

Table 2. Efficacy outcome measures at baseline (Full Analysis Set; mean±S.D. and t-test p-value)

	Silexan 160 mg/d (n=121)	Silexan 80 mg/d (n=135)	Paroxetine (n=132)	Placebo (n=135)	p (2-sided) i	ii	iii
HAMA total score[a]	26.0±4.5	25.8±4.8	25.8±4.9	25.1±4.7	0.22	0.12	0.21
CAS total score[b]	11.2±1.6	10.7±1.4	10.9±1.3	10.8±1.4	0.72	0.03	0.54
HAMD total score[c]	11.9±3.0	11.7±3.2	12.5±2.8	11.8±2.9	0.71	0.84	0.05
CGI Item 1 (severity of illness)[d]	4.6±0.7	4.7±0.6	4.6±0.6	4.6±0.6	0.30	0.68	0.58
SDS global impairment[e]	20.3±5.7	18.1±7.0	18.5±6.8	18.2±6.2	0.88	0.01	0.70
SF-36 physical health[f]	49.7±20.2	54.1±22.1	53.7±19.3	54.2±22.2	0.94	0.09	0.82
SF-36 mental health[f]	31.4±17.1	35.4±18.5	33.8±19.4	36.7±18.1	0.59	0.02	0.21

i Silexan 80 mg/d *vs.* placebo; ii Silexan 160 mg/d *vs.* placebo; iii paroxetine *vs.* placebo.
Theoretical ranges: [a]0–52; [b]3–15; [c]1–52; [d]1–7; [e]0–30; [f]0–100.
[a–e] Higher values indicate more severe impairment.
[f] Lower values indicate more severe impairment.
Abbreviations: HAMA – Hamilton Anxiety Scale; CAS – COVI Anxiety Scale; HAMD – Hamilton Depression Scale; CGI – Clinical Global Impressions Scale; SDS – Sheehan Disability Scale; SF-36 – SF-36 Health Survey Questionnaire.

subsequent visits. The treatment group difference between Silexan 80 mg/d and placebo became significant at Week 6 (mean value difference: 2.3 points; p=0.02) and remained significant until the end of randomized treatment. For paroxetine a borderline significant difference to placebo was observed after 6 wk (mean value difference: 1.8 points; p=0.06), and the p-values observed at Weeks 8 (p=0.16) and 10 (p=0.10) also exceeded the nominal level of descriptive significance. The average score reductions between the beginning and end of randomized treatment were 14.1±9.3 points for Silexan 160 mg/d, 12.8±8.7 points for Silexan 80 mg/d, 11.3±8.0 points for paroxetine, and 9.5±9.0 points for placebo. The results of the associated t-tests for the comparisons against placebo are shown in Table 3. The associated effect sizes were d=0.50 for Silexan 160 mg/d, d=0.37 for Silexan 80 mg/d, and d=0.21 for paroxetine. In confirmatory testing using ANCOVA models with the baseline HAMA total score as a covariate, the marginal means and associated 95% confidence intervals for the differences between Silexan and placebo were 4 points (1.9–6.1 points) for the 160 mg/d dosage (p<0.001, one-sided)

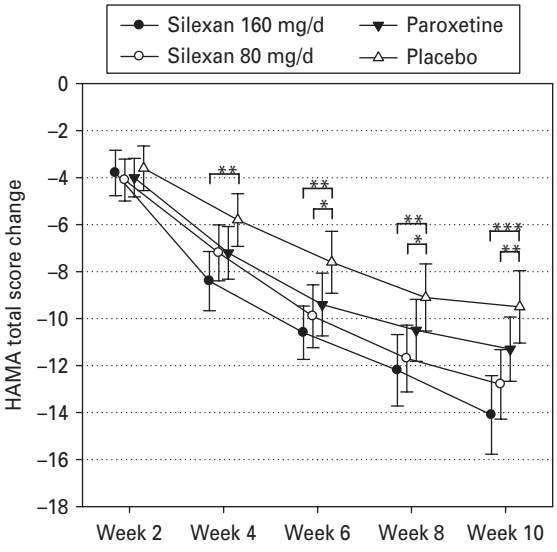

Fig. 2. HAMA total score change (full analysis set, means and S.D., last observation carried forward; HAMA: Hamilton Anxiety Scale; two-sided t-tests: *p<0.05, **p<0.01, ***p<0.001, angle brackets indicate which group was compared to placebo).

Table 3. Efficacy outcome measures change between baseline and treatment end (Full Analysis Set; mean±S.D. and *t*-test *p*-value; last post-baseline observation carried forward)

	Silexan 160 mg/d (n=121)	Silexan 80 mg/d (n=135)	Paroxetine (n=132)	Placebo (n=135)	*p* (2-sided) i	ii	iii
HAMA total score[a]	−14.1±9.3	−12.8±8.7	−11.3±8.0	−9.5±9.0	0.002	<0.001	0.096
HAMA somatic anxiety subscore[a]	−6.5±4.4	−5.9±4.4	−4.5±4.3	−4.5±4.8	0.015	<0.001	0.919
HAMA psychic anxiety subscore[a]	−7.7±5.4	−7.0±5.0	−6.7±4.7	−5.0±5.0	0.001	<0.001	0.004
CAS total score[a]	−5.2±3.1	−4.4±2.9	−4.0±2.7	−3.5±2.8	0.009	<0.001	0.117
HAMD total score[a]	−5.2±4.8 (n=119)	−4.1±5.0 (n=133)	−3.9±4.1 (n=130)	−2.8±4.7 (n=134)	0.024	<0.001	0.036
CGI Item 1 (severity of illness)[a]	−1.8±1.5	−1.5±1.3	−1.3±1.3	−1.0±1.3	0.005	<0.001	0.102
SDS global impairment[a]	−8.5±8.9 (n=118)	−7.1±8.1 (n=131)	−7.2±7.4 (n=125)	−5.0±7.4 (n=133)	0.026	<0.001	0.017
SF-36 physical health[b]	19.0±22.0 (n=118)	13.4±19.9 (n=131)	13.1±19.5 (n=125)	9.2±18.1 (n=133)	0.073	<0.001	0.095
SF-36 mental health[b]	28.2±26.8 (n=118)	22.3±24.5 (n=131)	22.5±22.8 (n=125)	14.4±23.5 (n=133)	0.008	<0.001	0.006

i Silexan 80 mg/d *vs.* placebo; ii Silexan 160 mg/d *vs.* placebo; iii paroxetine *vs.* placebo.
[a] Negative values denote improvement.
[b] Positive values denote improvement.
Abbreviations: see Table 2.

and 2.8 points (0.9–4.8 points) for the 80 mg/d dosage (p=0.003, one-sided), so that both null hypotheses were rejected. In the sensitivity analysis performed on the PPS the differences between Silexan and placebo were slightly more pronounced, with marginal means of 4.3 points (2.0–6.6 points) and of 3.5 points (1.5–5.6 points) for the differences between placebo and Silexan 160 and 80 mg/d, respectively (p<0.001, one-sided, for both comparisons). In the FAS, the patients treated with paroxetine showed a larger HAMA total score reduction than the participants in the placebo group, but the difference between the treatment groups was statistically not significant (Week 10: p=0.10, two-sided t-test). For the comparison between Silexan and paroxetine regarding HAMA total score decrease between baseline and treatment end marginal mean value differences (with 95% confidence intervals) of 2.8 points (0.7–4.9 points) and of 1.6 points (−0.3–3.5 points) were determined for the 160 mg/d dosage and the 80 mg/d dosage, respectively, in the FAS (positive differences favour Silexan).

Table 3 shows that the treatment group differences observed for the primary outcome measure were reflected on all secondary outcome measures as well. In the subscores of the HAMA both Silexan dosages were significantly superior to placebo, whereas paroxetine was superior to placebo regarding psychic anxiety but not somatic anxiety. According to the CAS anxiety and the HAMD rating scales as well as in the CGI, patients' self-ratings of global impairment (SDS) and general health (SF-36) all three pharmacologically active treatments show more pronounced improvements than placebo.

The percentage of patients who responded to treatment according to different criteria is shown in Fig. 3. According to the pre-specified HAMA criteria 73/121 patients in the Silexan 160 mg/d group (60.3%) were classified as responders and 56 (46.3%) were in remission, compared to 70/135 (51.9%) and 45 (33.3%) for Silexan 80 mg/d, 57/132 (43.2%) and 45 (34.1%) for paroxetine, and 51/135 (37.8%) and 40 (29.6%) in the placebo group. For the response criteria in Fig. 3 that are based on items 2 (global change) and 3.1 (therapeutic effect) of the CGI, the two-sided p-values for all active treatment comparisons against placebo were at or below 0.01.

Subgroup analyses by gender did not reveal any systematic differences regarding the response of female and male patients to the investigational treatments.

The analysis of efficacy in the FAS is influenced by the fact that the percentage of non-completers whose treatment end values had to be imputed from assessments performed earlier during randomized treatment was higher in the paroxetine group than in the case of Silexan or placebo (see Fig. 1). An observed cases (OC) analysis was, therefore, performed as an additional sensitivity analysis, which included all patients from the FAS for whom the assessments scheduled for the end of treatment week 10 were obtained without missing data imputation (placebo 120/135 patients in the FAS, 88.9%;

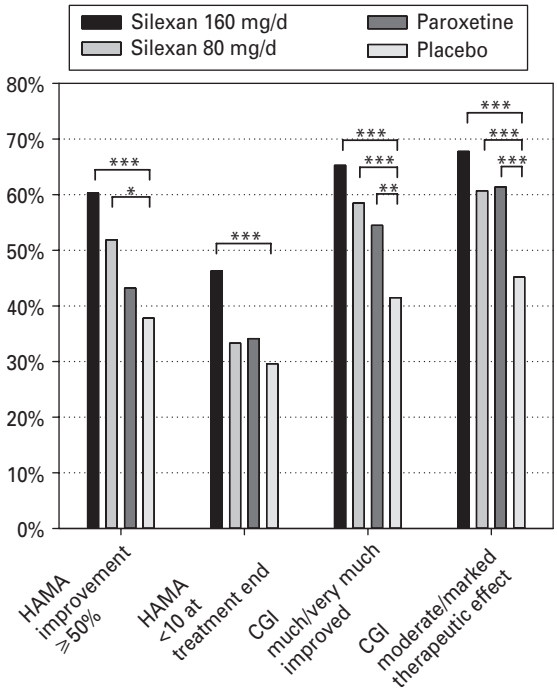

Fig. 3. Responder and remission rates (% of patients; full analysis set; HAMA: Hamilton Anxiety Scale; CGI: Clinical Global Impressions Scale; two-sided χ^2-tests: *$p<0.05$, **$p<0.01$, ***$p<0.001$, angle brackets indicate which group was compared to placebo).

Silexan 80 mg/ 119/135, 88.1%; Silexan 160 mg/d 109/121, 90.1%; paroxetine 180/132, 81.8%). For Silexan the results of the OC analysis (Table 4) fully support those of the primary analysis in the FAS (Table 3). For paroxetine the OC analysis confirms superiority over placebo regarding anxiety reduction (HAMA and CAS total score reduction: both $p<0.01$), global severity of impairment (self-rating, SDS; observer rating, CGI: both $p<0.05$)) as well as general health (SF-36 mental health subscore: $p<0.01$; two-sided *t*-tests).

Safety/tolerability

During randomized treatment 32/128 patients randomized to Silexan 160 mg/d (25.0%) reported 48 adverse events (AEs), 47/135 patients in the Silexan 80 mg/d group (34.8%) had 71 AEs, 56/137 treated with paroxetine (40.9%) experienced 89 AEs, and 42/136 patients in the placebo group (30.9%) reported 73 AEs. The incidence densities were 0.006 AEs/d of exposure for Silexan 160 mg/d, 0.008 AEs/d for the 80 mg/d dosage, 0.011 AEs/d for paroxetine, and 0.008 AEs/d for placebo. Gastrointestinal disorders, infections, and nervous system disorders were the most common adverse events across all study groups.

Among all system organ classes the only class for which a more than 3% increase (risk difference) in any Silexan group over placebo was observed was gastrointestinal disorders (risk difference to placebo with 95% confidence interval: Silexan 160 mg/d 4.4% (−3.0–12.1%), 80 mg/d 4.5% (−2.9–12.0%), paroxetine 8.0% (0.2–15.9%)). Compared to paroxetine the rates of patients with AEs were 15.9% (4.5–26.6%) and 6.1% (−5.4–17.3%) lower for 160 and 80 mg/d, respectively (risk differences).

A total of five serious adverse events were reported during and up to one month after randomized treatment (Silexan 160 mg/d 2; 80 mg/d 2; paroxetine 1). The causal relationship to the investigational treatment of all of these events was considered not related or unlikely.

During down-titration no withdrawal related adverse events were observed in any of the treatment groups. A total of 418 patients (Silexan 160 mg/d 97, 80 mg/d 115, paroxetine 101, placebo 105) met the criteria for the analysis of withdrawal symptoms using the PWC 20 scale. Between the assessments performed at the end of randomized treatment and at the end of the down-titration phase none of the treatment groups exhibited an increase in the mean or median PWC 20 total score or in the average number of potentially withdrawal-related symptoms.

Discussion

The study demonstrates that the lavender oil preparation Silexan, at daily doses of 160 or 80 mg given for 10 wk, is efficacious in reducing the cardinal symptoms of anxiety in patients suffering from GAD. The results are consistent with previous research in patients with subsyndromal anxiety disorder (Kasper et al., 2010b, c). Both investigated dosages of Silexan also significantly improved the patients' mental condition in general and had a beneficial effect on health-related quality of life. Furthermore, the drug also had a profound beneficial effect on depressive co-morbidity.

For the HAMA total score Fig. 2 shows that the time courses of recovery from GAD in all treatment groups resembled exponentially shaped curves, albeit with different slopes so that the differences between the groups tended to increase over time. Exponentially shaped recovery curves have been observed in other psychiatric conditions as well, for example, in major depression (Friede et al., 2000). In the present trial only negligible treatment group differences for change from baseline were observed after the first 2 wk of randomized treatment, but Silexan 160 mg/d had a significant effect compared to placebo already after 4 wk whereas the difference between Silexan 80 mg/d and placebo became significant after 6 wk and remained significant until the end of randomized treatment.

Beyond the primary objective of the trial of demonstrating superiority in efficacy over placebo, the trial also shows, on a descriptive level, that Silexan was at least as efficacious as paroxetine, one of the drugs currently recommended as first-line treatment in GAD (Bandelow et al., 2008). The average HAMA total score

Table 4. Efficacy outcome measures change between baseline and week 10 (Observed Cases analysis; mean ± S.D. and *t*-test *p*-value; no missing data imputation)

	Silexan 160 mg/d (n=109)	Silexan 80 mg/d (n=119)	Paroxetine (n=108)	Placebo (n=120)	*p* (2-sided)		
					i	ii	iii
HAMA total score[a]	−15.5±6.8	−14.4±7.8	−13.3±7.0	−10.5±6.8	<0.001	<0.001	0.008
HAMA somatic anxiety subscore[a]	−7.1±4.2	−6.6±4.2	−5.4±4.0	−4.9±4.5	0.003	<0.001	0.347
HAMA psychic anxiety subscore[a]	−8.4±5.1	−7.8±4.5	−7.8±4.3	−5.6±4.8	<0.001	<0.001	<0.001
CAS total score[a]	−5.7±2.8	−4.9±2.7	−4.8±2.3	−3.8±2.8	0.002	<0.001	0.004
CGI Item 1 (severity of illness)[a]	−1.9±1.4	−1.6±1.3	−1.5±1.3	−1.1±1.3	0.005	<0.001	0.018
SDS global impairment[a]	−9.8±8.9 (n=92)	−8.4±8.1 (n=108)	−8.1±7.2 (n=101)	−5.7±7.3 (n=111)	0.011	<0.001	0.016
SF-36 physical health[b]	20.0±22.5 (n=108)	15.4±20.5	15.2±20.0	10.7±17.8	0.060	<0.001	0.072
SF-36 mental health[b]	30.7±27.0 (n=108)	24.7±25.2 (n=118)	25.8±22.2	16.7±23.8	0.012	<0.001	0.003

i Silexan 80 mg/d *vs.* placebo; ii Silexan 160 mg/d *vs.* placebo; iii paroxetine *vs.* placebo.
[a] Negative values denote improvement.
[b] Positive values denote improvement.
Abbreviations: see Table 2.

reductions by 13 and 14 points after 10 wk of treatment were also in the range of the score reductions published for anxiolytic drugs like bromazepam, oxazepam (Woelk et al., 1999), escitalopram (Bielski et al., 2005) and duloxetine (Allgulander et al., 2007) in the same therapeutic indication, although treatment periods between 6 and 24 wk were used in these trials. Hidalgo et al. (2007) performed a meta-analysis of 21 double-blind, placebo-controlled trials in patients with GAD. Based on HAMA total score change *vs.* baseline they determined average effect sizes *vs.* placebo of 0.50 for pregabalin, 0.45 for hydroxyzine, 0.42 for venlafaxine, 0.38 for all benzodiazepines (alprazolam, diazepam, lorazepam, 0.36 for all SSRIs (paroxetine, sertraline, fluvoxamine, escitalopram), and 0.17 for buspirone. The effect sizes of 0.37 and 0.50 observed for the comparisons between Silexan 80 and 160 mg/d with placebo in this trial were comparable to the SSRIs' effect size in Hidalgo and coworkers' review (Hidalgo et al., 2007).

Both dosages of Silexan were found to be safe in use. Unlike paroxetine, the observed AE rates for Silexan did not exceed those reported during treatment with placebo.

This was the first randomized, reference- and placebo-controlled trial that investigated the efficacy of Silexan in GAD. Effect size estimates were obtained both in comparison to placebo and paroxetine, the latter of which is among the recommended first line treatments in this indication. In this experimental setting Silexan demonstrated convincing anxiolytic efficacy as well as a favourable safety profile, and the results were fully supported by sensitivity analyses performed in patients with and without serious protocol violations as well as with and without missing data imputation.

The interpretation of the results of the primary analysis in the FAS for the active comparator paroxetine was influenced by a larger number of premature withdrawals in this group as compared to Silexan and placebo. The observed cases (OC) analysis shows that the effect of paroxetine was probably somewhat underestimated in the FAS, since less favourable outcomes of patients prematurely withdrawn had to be carried forward to a greater extent than in the other groups. Particularly in the OC analysis, paroxetine demonstrated a clinically meaningful anxiolytic effect that was comparable to what has been published elsewhere for this compound (Bielski et al., 2005; Hidalgo et al., 2007), which in turn supports the assay sensitivity of this trial in general. Moreover, although 20 mg/d is the recommended dosage of paroxetine in GAD, some of the patients randomized to the SSRI may have required a higher dosage in order to obtain a satisfactory anxiolytic effect.

A recently completed study sheds light on the drug's molecular mechanism of action and will certainly stimulate future research: Schuwald et al. (2013) administered Silexan to mice, using nanomolar concentrations corresponding to therapeutic doses in humans, and compared the results to those after administration of pregabalin or

diazepam and to an untreated control group. In the elevated plus maze test Silexan showed a comparable anxiolytic effect to that of pregabalin and diazepam. Furthermore, the herbal oil was found to be a potent inhibitor of voltage dependent calcium channels (VOCCs) in synaptosomes, primary hippocampal neurons and stably over-expressing cell lines, where it showed an effect comparable to that of pregabalin. Silexan did, however, not primarily bind to P/Q type calcium channels and did not interact with the binding site of pregabalin, the a2δ subunit of VOCCs. The herbal oil caused a non-selective reduction of the calcium influx through N-type, P/Q-type and T-type VOCCs. The results explain the drug's inhibitory effect of Silexan in the hippocampus, a brain region important for anxiety disorders, but also indicate that human data obtained with brain imaging techniques will be necessary to confirm these promising results in man.

In conclusion, the trial demonstrates that Silexan is efficacious and well tolerated in patients with GAD, also at the higher dosage of 160 mg/d. The drug can be terminated after 10 wk of treatment with the full therapeutic dose without down-titration and without causing symptoms of withdrawal. It could, therefore, be a well-tolerated option in the treatment of GAD.

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Conflicts of Interest

Professor Dr Kasper has received grant/research support from Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, Organon, Schwabe, 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, Sepracor, Servier, Pierre Fabre, and Janssen.

Professor Dr Gastpar has served as member of advisory boards for Astra-Zeneca, Lundbeck, Schwabe, Servier and Wyeth and on speaker's bureaus of Servier and Schwabe.

Professor Dr Müller received grant support from Sanofi-Aventis, UCB, Schwabe, CasellaMed and Novartis. He works as consultant for Bayer, Boehringer Ingelheim, CasellaMed, Jansson-Cilag, Lundbeck, Pfizer, Organon, Schwabe, UCB and Wyeth. As speaker he recently gave scientific presentations for Astra-Zeneca, Glaxo Smith Kline, Lundbeck, Pfizer, Eli-Lilly, UCB, Schwabe, Jansson-Cilag, Bristol Myers Squibb and Novartis.

Professor Dr Volz has served as a consultant or on advisory boards for Astra/Zeneca, Eli Lilly, Lundbeck, Pfizer, Schwabe, Janssen, Otsuka, Merz, Wyeth and has serves on speakers' bureaus for Astra/Zeneca, Eli Lilly, Lundbeck, Schwabe, Janssen, Merz, Wyeth. Lichtwer, Steigerwald, Hormosan, and Bristol-Myers Squibb.

Professor Dr Möller has received grants or is a consultant for and on the speakership bureaus of AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Schwabe, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Sepracor, Servier and Wyeth.

Dr Dienel and S. Schläfke are employees of Dr Willmar Schwabe GmbH & Co. KG

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