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Efficacy and safety of silexan, a new, orally administered lavender oil preparation, in subthreshold anxiety disorder – evidence from clinical trials

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Wirksamkeit und Verträglichkeit von Silexan, einer neuen, oral verabreichten Zubereitung aus Lavendelöl, bei subsyndromaler Angststörung – Evidenz aus klinischen Prüfungen

Zusammenfassung. Diese Übersichtsarbeit untersucht die Wirksamkeit und Verträglichkeit von Silexan, einer neuartigen Zubereitung aus Lavendelöl zur oralen Anwendung, bei der Behandlung von Angsterkrankungen und verwandten Krankheitsbildern unter besonderer Berücksichtigung unterschwelliger Angststörungen.

Es wurden 3 randomisierte Doppelblindstudien identifiziert, die die anxiolytische Wirksamkeit von Silexan bei subsyndromaler Angststörungen (*vs.* Plazebo; Behandlungsdauer 10 Wochen), bei generalisierten Angststörungen (GAS, *vs.* Lorazepam; 6 Wochen) und bei Unruhe und Agitiertheit (*vs.* Plazebo; 10 Wochen) gemäß DSM-IV- und ICD-10-Kriterien untersuchten. Zur Messung des Angstniveaus dienten die Hamilton Angstskala (HAMA).

Insgesamt erhielten 280 Patienten 80 mg/Tag Silexan; 37 wurden mit 0,5 mg/Tag Lorazepam und 192 mit Placebo behandelt. Bei Behandlungsbeginn lag der HAMA-Gesamtwert in den Behandlungsgruppen zwischen 24,7 und 27,1 Punkten. Unter Silexan zeigten sich Abnahmen zwischen $10{,}4 \pm 7{,}1$ und $12{,}0 \pm 7{,}2$ Punkten nach 6 Wochen und zwischen $11{,}8 \pm 7{,}7$ und $16{,}0 \pm 8{,}3$ Punkten nach 10 Wochen. Bei Patienten mit GAS war die HAMA-Gesamtwert-Abnahme unter Silexan und Lorazepam vergleichbar (90 % KI für die Mittelwertsdifferenz: −2,3; 2,8 Punkte).

Schlüsselwörter: Angsterkrankung, Silexan, Wirksamkeit, Verträglichkeit, klinische Studien

Summary. We review the data on the efficacy and tolerability of silexan, a novel preparation from lavender oil for oral use, in the treatment of anxiety disorders and related condition with particular attention to subthreshold generalized anxiety disorder (GAD).

Three randomized, double-blind clinical trials were identified which investigated the efficacy of silexan in subsynromal anxiety disorder (*vs.* placebo; 10 weeks' treatment), in GAD (*vs.* lorazepam; 6 weeks), and in restlessness and agitation (*vs.* placebo; 10 weeks) according to DSM-IV and ICD-10 criteria. All trials assessed the participants' anxiety levels using the Hamilton Anxiety Scale (HAMA).

Across all trials 280 patients were exposed to silexan 80 mg/day, 37 were treated with lorazepam 0.5 mg/day and 192 received placebo. Average within group HAMA total scores at baseline ranged between 24.7 and 27.1 points. Patients treated with silexan showed average HAMA total score decreases by between 10.4 ± 7.1 and 12.0 ± 7.2 points at week 6 and by between 11.8 ± 7.7 and 16.0 ± 8.3 points at week 10. In GAD silexan and lorazepam showed comparable HAMA total score reductions (90% CI for mean value difference: −2.3; 2.8 points).

Key words: Anxiety disorder, silexan, efficacy, safety, clinical trials

Introduction

According to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)

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published in 1994 [1], a diagnosis of generalized anxiety disorder (GAD) requires the presence of excessive anxiety and worry (a) for at least 6 months, (b) that the person finds difficult to control, and (c) that are associated with at least three of the six symptoms restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance. Furthermore, (d) the focus of anxiety and worry must not be confined to features of other (named) psychiatric disorders, they have to (e) cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, and (f) they must not be attributable to the physiological effects of substance (ab)use.

Material and methods

In clinical practice physicians or psychologists are often faced with individuals who meet several, but not all of the criteria required for a diagnosis of GAD, but who nevertheless experience considerable psychological strain and suffering. In a community study performed in Germany Carter and colleagues [2] estimated a prevalence rate of strictly defined, 12-month DSM-IV GAD of 1.5%; however, 3.6% of the 4181 respondents presented with at least some, but not all of the symptoms of GAD according to DSM-IV criteria during the past 12 months. Cohen and colleagues [3] observed prevalence rates of 2.3% for DSM-IV compliant GAD and of 13.3% for patients with several but not all symptoms in an epidemiological study in the U.S.A. with 1.074 elderly participants. Also in elderly subjects Heun and co-workers [4] determined a lifetime prevalence of 6.6% for major anxiety disorders and of 18.5% for anxiety disorders not meeting all of the required diagnostic criteria. Wittchen and colleagues [5] screened over 20,000 patients in German primary care practices and found GAD rates between 2.4% and 7.0% depending on age. However, the rate of patients who had anxiety symptoms meeting the DSM-IV criteria for GAD, but with shorter duration, ranged between 19.3% and 23.2%.

These results suggest that in a considerable number of patients clinically significant symptoms of anxiety are present, but a formal diagnosis is not assigned because the number or the duration of symptoms does not reach the diagnostic threshold. Accordingly, such conditions are often described as subthreshold or subsyndromal GAD [6] that is classified as anxiety disorder not otherwise specified (NOS) under the current diagnostic systems [7]. To date there appears to be no generally accepted definition of subthreshold GAD. Whereas most researchers require fewer symptoms than in the DSM-IV definition or question the criterion of a minimum duration of six months (e.g. [2, 4, 8, 9]), others focus on lower minimum scores on psychiatric scales assessing anxiety or worries (e.g. [3]). Different working definitions of subthreshold GAD are likely to explain differences between published prevalence rates, although most reports indicate that the rate of subthreshold pathology is at least three times as high as in case of threshold anxiety disorder.

Although by definition subthreshold anxiety conditions, that are particularly common in primary care settings, do not meet all criteria of GAD according to the DSM-IV definition, they are nevertheless associated with significant suffering and functional impairment, and should therefore not be confused with subclinical presentations that lack interference and distress [10]. Indeed, Kessler and colleagues [8] observed that patients who failed to meet the full criteria for GAD had similar levels of functional impairment than those with a threshold level disorder. Like GAD, subthreshold anxiety is associated with a high risk of co-morbidity [11] (e.g. dysthymia and chronic pain) and with a low rate of spontaneous remission [12]. It affects quality of life and working capacity more adversely than major depressive disorder [13]. These findings underline that subthreshold GAD is a serious disease requiring treatment. Furthermore, there is evidence that adequate treatment of subthreshold anxiety may help to prevent the evolution of a disorder at the syndromal level [6, 14–16].

As there is no uniform definition of subthreshold anxiety disorder it is not surprising that no specific guidelines for the treatment of subsyndromal cases have been developed yet, and in fact many of these patients do not receive any treatment [3]. One of the reasons for this observation may be that subthreshold anxiety is not always recognized by primary care physicians as condition in need of therapy. However, there is also evidence that patients are reluctant to take, or physicians are reluctant to prescribe, drugs like benzodiazepines, antidepressants and neuroleptics that may cause burdensome side effects (e.g. nausea, dizziness, sedation and sexual dysfunction) which can seriously interfere with essential activities of daily living (e.g. the ability to drive or to operate machinery), or have an addictive potential [17–19]. Therefore there is a need for efficacious and well-tolerated medicinal products with a favorable risk-benefit ratio specifically in patients with anxiety disorder of subthreshold intensity.

In this article we review the results of clinical trials investigating the efficacy and tolerability of silexan[1], a novel herbal medicinal product from lavender oil in an immediate release capsule for oral administration, in anxiety disorder. Recently the medicinal product has been authorized in Germany for the treatment of restlessness states accompanying anxious mood.

The following sections present preclinical and early clinical experience with silexan as well as data from therapeutic trials in anxiety. We close with a discussion.

Results

Pharmacology and preclinical results

Silexan is an essential oil produced from fresh Lavandula angustifolia flowers by steam distillation. As a basic requirement, the quality-selected, well-defined preparation complies with the monograph Lavender oil of the European Pharmacopeia [20] with respect to all quality parameters.

Lavender oil is a multi ingredient mixture that contains more than 160 substances. The main constituents are linalool, linalyl acetate, 1.8-cineole, β-ocimene, terpinen-4-ol and camphor. In man the therapeutic effect of the polypharmaceutical medicinal product has been investigated only as a whole [21]. In animal models linalool was found to inhibit the glutamate binding in the cerebral cortex, an effect that has been suggested to contribute to the action of lavender oil on the central nervous system [22]. In the elevated Plus Maze test the anxiolytic effect of silexan was comparable to that of diazepam and pergabalin.

Animal studies[2] with silexan showed no evidence of a teratogenic effect or for an impairment of fertility or fetal development. In chronic toxicity studies the No Observed Effect Level (NOEL) was about 200-fold higher than the recommended dose in humans. Tests for genotoxic effects and mutagenicity were negative. No adverse effects on cardiovascular, central nervous or respiratory functions were observed.

Silexan is available in soft gelatin capsules that contain 80 mg of essential oil; it is currently the only pharmaceutical quality lavender oil preparation for oral use.

Pharmacokinetic, toxicology and food interaction studies[3]

Pharmacokinetic studies performed with silexan demonstrate a rapid absorption and elimination of linalool with $t_{1/2}$ at about 4 hours after a single dose and about 9 hours after 14 days of once daily administration. During multiple dosing a steady state was achieved after about 5 days. The data indicate only a mild cumulation effect that did not raise any safety concerns.

The bioavailability of silexan was not relevantly modified by preceding food intake.

While the recommended therapeutic dose of silexan is 80 mg once daily studies in healthy volunteers included single doses of up to 640 mg and multiple doses of up to 320 mg/day given for 14 days. The most frequent adverse reaction after intake of higher than therapeutic doses was by eructation. The results indicate a large safety margin of the recommended therapeutic dose.

Clinical efficacy

Unless otherwise indicated this section reports the results obtained in the full analysis set (FAS) of the trial. All p-values are two-sided.

Overview

Our review includes the data from 3 randomized, controlled trials and an open, non-comparative pilot study investigating the efficacy and tolerability of silexan in anxiety disorder and related conditions. The main characteristics of these trials are presented in Tab. 1.

Trials I [23] and II [24] were randomized, controlled studies in anxiety disorder NOS and GAD according to DSM-IV diagnostic criteria. Trial III [25] investigated the effect of silexan on restlessness and agitation that are among the direct symptoms of GAD. The participants of this trial were patients who were suffering from other symptoms associated with GAD as well, albeit without fulfilling all of the criteria required for a diagnosis of GAD. Whereas Trials I and III were performed to demonstrate superiority in efficacy of silexan over placebo, Trial II was aimed at comparing the effects of silexan to the benzodiazepine lorazepam. In pilot study IV [26, 27] the effect of the herbal remedy in neurasthenia, posttraumatic stress disorder (PTSD) and somatization disorder was assessed as states of anxiety are among the manifestations of these conditions. The study also assessed other direct symptoms of neurasthenia and PTSD that

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

[2] Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany: unpublished data.

[3] Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany: unpublished data.

Tab. 1: Main characteristics of studies included in the review

Study	I	II	III	IV
Publication	Kasper et al. [23]	Woelk and Schläfke [24]	Kasper and Dienel [25]	Stange et al. [26, 27]
Design	Double-blind, randomized, placebo controlled multicenter trial	Double-blind, double-dummy, randomized, reference controlled multicenter trial	Double-blind, randomized, placebo controlled multicenter trial	Open, non-comparative, monocenter pilot study
Diagnosis for inclusion	Anxiety disorder not otherwise specified (DSM-IV 300.00)	Generalized anxiety disorder (DSM-IV 300.02)	Restlessness and agitation (ICD-10 R45.1)	Neurasthenia (ICD-10 F48.0), posttraumatic stress disorder (F43.1), or somatization disorder (F45.0, F45.1)
No. of patients, interventions	1 × 80 mg/day silexan ($n = 107$) or placebo ($n = 109$), 10 weeks	1 × 80 mg/day silexan ($n = 40$) or 1 × 0,5 mg/day lorazepam ($n = 37$), 6 weeks	1 × 80 mg/day silexan ($n = 86$) or placebo ($n = 84$), 10 weeks	1 × 80 mg/day silexan ($n = 50$), 6 weeks
Main efficacy outcome measures	Hamilton Anxiety Scale (HAMA); Zung Self-rating Anxiety Scale (SAS); Pittsburgh Sleep Quality Index (PSQI); SF-36 Health Survey Questionnaire; Clinical Global Impressions (CGI)	Hamilton Anxiety Scale (HAMA); Zung Self-rating Anxiety Scale (SAS); sleep diary; SF-36 Health Survey Questionnaire; Clinical Global Impressions (CGI)	Hamilton Anxiety Scale (HAMA); Zung Self-rating Anxiety Scale (SAS); Pittsburgh Sleep Quality Index (PSQI); State Check; Clinical Global Impressions (CGI)	State Check; State-Trait Anxiety Inventory (STAI); sleep diary; Symptom Checklist (SCL-90-R); SF-36 Health Survey Questionnaire

are not presented in this paper because of its focus on subthreshold anxiety.

Table 2 provides a summary of the demographic and baseline characteristics of the FAS. In trial IV 27 patients (57.5% of 47) suffered from neurasthenia, 30 (63.8%) had posttraumatic stress syndrome and 9 (19.1%) were diagnosed to have a somatization disorder (multiple responses).

Anxiolytic efficacy

In Trials I, II and III, the change in the HAMA total score between baseline and treatment end was used as a primary outcome measure for treatment efficacy.

Figure 1 shows the time course of the HAMA total score during randomized treatment. Patients treated with silexan showed average score decreases by 12.0 ± 7.2 points, by 11.3 ± 6.7 points, and by 10.4 ± 7.1 points (mean ± SD) during the first 6 weeks in Trials I, II and III, respectively. During the same period HAMA total score decreases of 8.2 ± 7.9 points and of 8.1 ± 7.9 points were observed in the placebo group in Trials I and III, and of 11.6 ± 6.6 points in the lorazepam control group in Trial II. In the studies that included a 10-week treatment period, the over-all HAMA total score reductions for silexan and placebo at treatment end were 16.0 ± 8.3 *vs.* 9.5 ± 9.1 points in Trial I (95% confidence interval for mean value difference: 4.1; 8.8 points; *t*-test: $p < 0.01$) and 11.8 ± 7.7 *vs.* 9.6 ± 8.7 points in Trial III ($p = 0.08$). In Trial II the 90% confidence interval for the HAMA total score reduction mean value difference at week 6 ranged from 2.8 points in favor of lorazepam to 2.3 points in favor of silexan.

In Trials I through III anxiolytic treatment response was defined as a reduction of the HAMA total score at treatment end by at least 50% of the value determined at baseline. According to this definition the HAMA responder rates after 10 weeks of treatment were 76.9% for silexan and 49.1% for placebo in Trial I (in trial I response was defined as at least 50% reduction of HAMA total score or PSQI total score), and 48.4% and 33.3% in Trial III, respectively. In Trial II responder rates of 52.5% and 40.5% were determined for silexan and lorazepam, respectively, after 6 weeks of treatment. Figure 2 shows the differences between the treatment groups' responder rates as well as the associated 95% confidence intervals. Whereas the confidence intervals for Trials I and III indicate systematic superiority of silexan responder rates over placebo, the results in Trial II show a descriptive advantage of silexan over lorazepam by a rate difference of 12% and exclude a rate difference of more than 10% against the herbal essence with a probability of 95%.

Tab. 2: Baseline characteristics (full analysis set; patients (%), or mean ± SD)

		Silexan	Control[§]	*p*
Trial I	*N*	104	108	
	Sex: female patients	76 (73.1%)	83 (76.9%)	0.53[a]
	Age (years; median, 1st–3rd quartile)	46 (38–54)	46.5 (45–56)	0.55[b]
	HAMA total score	26.8 ± 5.4	27.1 ± 5.3	0.76[b]
	PSQI total score	12.3 ± 2.9	12.6 ± 3.0	0.51[b]
	Zung SAS total score	60.1 ± 9.9	61.1 ± 10.1	0.45[b]
	SF-36 mental health	32.3 ± 17.4	32.6 ± 21.2	0.90[b]
	CGI item 1 – markedly or severely ill	62 (59.6%)	73 (67.6%)	0.05[c]
Trial II	*N*	40	37	
	Sex: female patients	33 (82.5)	26 (70.3)	0.28[a]
	Age (years; median, 1st–3rd quartile)	52 (41–57)	47 (35–56)	0.26[a]
	HAMA total score	24.9 ± 3.7	24.7 ± 3.7	0.86[b]
	Zung SAS total score	61.4 ± 6.6	61.5 ± 5.5	0.95[b]
	SF-36 mental health	39.9 ± 15.9	36.5 ± 13.0	0.31[b]
	CGI item 1 – markedly or severely ill	20 (50.0%)	19 (51.4%)	0.91[c]
Trial III	*N*	86	84	
	Sex: female patients	62 (72.1%)	60 (71.4%)	0.93[a]
	Age (years; median, 1st–3rd quartile)	49 (41–57)	48 (35.5–57.5)	0.57[a]
	HAMA total score	25.5 ± 6.0	26.5 ± 6.1	0.27[b]
	PSQI total score	12.2 ± 2.5	12.7 ± 2.8	0.19[b]
	Zung SAS total score	54.5 ± 12.3	55.9 ± 10.3	0.43[b]
	CGI item 1 – markedly or severely ill	49 (57.0%)	46 (54.8%)	0.51[a]
Trial IV	*N*	47		
	Sex: female patients	39 (83.0%)		
	Age (years; median, 1st–3rd quartile)	52 (46–59)		
	STAI, State Anxiety	46.2 ± 10.8		
	STAI, Trait Anxiety	53.9 ± 7.8		
	SF-36 mental health	39.0 ± 15.5		

[§] Control treatment: Trials I and III – placebo; Trial II – lorazepam.
HAMA Hamilton Anxiety Scale; *PSQI* Pittsburgh Sleep Quality Index; *SAS* Zung Self-rating Anxiety Scale; *SF-36* SF-36 Health Survey Questionnaire; *CGI* Clinical Global Impressions; *STAI* State-Trait Anxiety Inventory.
For the HAMA, STAI, PSQI, and the SAS, higher scores indicate more severe impairment whereas lower scores indicate more severe impairment for the SF-36.
[a] χ^2-test; [b] *t*-test; [c] Mantel-Haenszel-χ^2-test for original data.

As a patient reported outcome the results of the Zung Self-rating Anxiety Scale (SAS) [28] administered in Trials I through III complete those of the observer rated HAMA. In Trials I and III the SAS total score was reduced by 15.6 ± 11.4 and by 11.2 ± 10.1 points for silexan and by 11.1 ± 12.2 points and by 9.3 ± 10.4 for placebo, respectively (Trial I: $p < 0.01$; Trial II: $p = 0.24$). The participants of Trial II reported average SAS total score decreases of 14.8 ± 11.4 and 14.4 ± 8.5 points for silexan and lorazepam, respectively (90% confidence interval for mean value difference, silexan – lorazepam: −3.4; 4.2 points).

In Trial IV the participants' anxiety level was assessed using the State-Trait Anxiety Inventory (STAI,

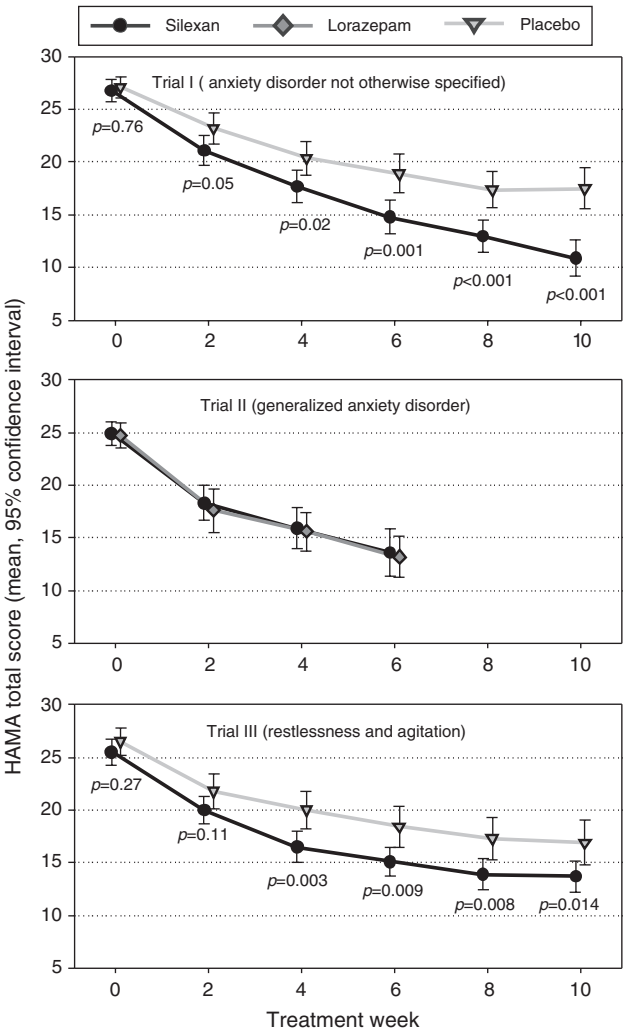

Fig. 1: Hamilton Anxiety Scale time course (full analysis set; last observation carried forward)

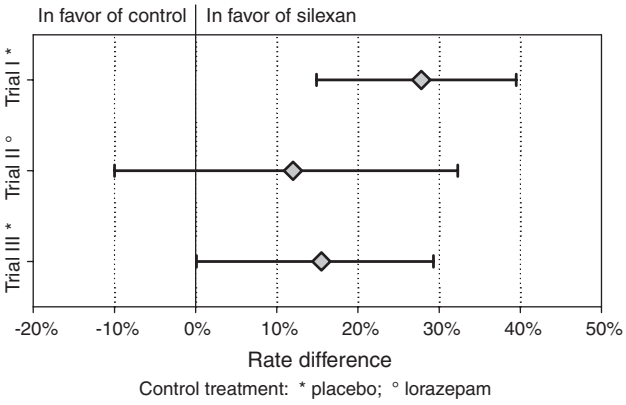

Fig. 2: Responder rates (decrease of Hamilton Anxiety Scale ≥50% compared to baseline) – rate difference between silexan and control treatment (with 95% confidence interval)

[29]). During 6 weeks' treatment with silexan the patients exhibited an average reduction of the state anxiety subscore by 4.5 ± 10.7 points (or 9.7% of the baseline mean score) and a reduction of the trait anxiety subscore by 7.4 ± 8.9 points (13.7% of the baseline mean value; change versus baseline, both subscores, Wilcoxon signed rank test: $p < 0.01$).

Effects on restlessness and sleep

Restlessness was assessed in Trials III and IV as a part of the State Check inventory, a compilation of one-item measures assessing the severity and the extent of change of several direct symptoms of GAD. In Trial III 86.1% of the patients in the silexan group (74 of 86) and 90.5% in the placebo group (76 of 84) felt often or always restless at baseline. By the end of randomized treatment at week 10 these rates decreased to 28.0% (24 of 86) for silexan and to 41.7% (35 of 84) for placebo (treatment group comparison, Mantel-Haenszel-χ^2-test: $p < 0.01$). At baseline in Trial IV 83.0% of the participants (39 of 47) described themselves as often or always restless. By the end of the trial after 6 weeks 29 of the 47 patients (61.7%) were improved (change versus baseline, Wilcoxon signed rank test: $p < 0.01$).

In Trials I and III the change of the total score of the Pittsburgh Sleep Quality Index (PSQI) [30] was introduced as a co-primary endpoint. Table 3 shows that in anxiety disorder NOS (Trial I) the improvements of sleep quality in the silexan group were significantly more pronounced than in those treated with placebo. By comparison, Trial III, whose patients were primarily suffering from restlessness and agitation, showed similar improvements of sleep quality versus baseline, but only a negligible treatment effect of silexan.

The assessment of sleep quality in Trials II and IV was based on a sleep diary which the patients had to maintain on a daily basis. Compared to baseline, the patients in Trial IV reported an increase in total sleep time ($p = 0.08$, Wilcoxon signed rank test) although bed time changed only marginally. Waking-up frequency ($p < 0.01$) and duration ($p < 0.01$) were reduced and sleep was more efficient ($p = 0.04$). In the morning the study participants were on average less tired ($p = 0.01$) and in an improved mood ($p = 0.06$). During double-blind treatment the participants of Trial II experienced similar improvements of sleep related measures. None of the items of the sleep diary showed significantly different changes from baseline in the silexan group and in patients treated with lorazepam.

Activities of daily living, quality of life

The 36-item Short Form Health Survey Questionnaire (SF-36, [31]) assesses a broad spectrum of general health concepts (limitations in physical activities due

Tab. 3: Secondary efficacy outcome measures: change between baseline and end of treatment (full analysis set; patients (%), or mean ± SD)

		Silexan	Control[§]	*p* or 95% CI
Trial I	*N*	104	108	
	PSQI total score	–5.5 ± 4.4	–3.8 ± 4.1	< 0.01[b]
	SF-36 physical health	20.5 ± 22.6	10.8 ± 19.8	< 0.01[b]
	SF-36 mental health	32.5 ± 24.1	19.8 ± 22.4	< 0.01[b]
	CGI item 1 – not at all ill/borderline mentally ill	51 (49.0%)	21 (19.4%)	< 0.01[c]
	CGI item 2 – marked/moderate improvement	77 (74.0%)	44 (40.7%)	< 0.01[c]
Trial II	*N*	40	37	
	SF-36 physical health	12.5 ± 17.4	16.9 ± 18.0	[–11.6; 2.6]
	SF-36 mental health	21.2 ± 18.6	24.3 ± 18.7	[–10.4; 4.2]
	CGI item 1 – not at all ill/borderline mentally ill	3 (7.5%)	3 (8.1%)	0.79[c]
	CGI item 2 – marked/moderate improvement	28 (70.0%)	19 (51.4%)	0.49[c]
Trial III	*N*	86	84	
	PSQI total score decrease, week 10 *versus* baseline	–4.8 ± 4.0	–4.3 ± 4.5	0.48[b]
	CGI item 1 – not at all ill/borderline mentally ill	17 (19.8%)	12 (14.3%)	0.08[c]
	CGI item 2 – marked/moderate improvement	45 (52.3%)	27 (32.1%)	0.06[c]
Trial IV	*N*	47		
	SF-36 physical health	8.3 ± 16.6		
	SF-36 mental health	18.8 ± 22.3		

[§] Control treatment: Trials I and III – placebo; Trial II – lorazepam.
PSQI Pittsburgh Sleep Quality Index; *SF-36* SF-36 Health Survey Questionnaire; *CGI* Clinical Global Impressions.
[a] χ^2-test; [b] *t*-test; [c] Mantel-Haenszel-χ^2-test for original data.

to health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical or emotional health problems; bodily pain; general mental health; vitality; general health perceptions) with implications on activities of daily living and quality of life. Table 3 shows that in patients suffering from anxiety disorder NOS (Trial I) the improvements of both mental and physical health factors in the silexan group were substantially more pronounced than in those treated with placebo. The improvements observed in the items of the SF-36 in Trial II (GAD) were generally less pronounced than in Trial I; however, the shorter treatment period in Trial II (6 *vs.* 10 weeks) has to be taken in consideration. Trial II did not indicate systematic differences in SF-36 improvement between silexan and lorazepam although the changes observed in the lorazepam group were descriptively somewhat more pronounced.

Clinical global impressions

According to Item 1 (severity of mental illness) of the Clinical Global Impressions (CGI) questionnaire [32], the percentage of patients treated with silexan with no or only minimal residual pathology at treatment end was higher in study participants with anxiety disorder NOS (Trial I) than in GAD (Trial II) or in those with prominent restlessness and anxiety (Trial III). A comparison between Tab. 2 and 3 shows that this effect cannot be explained by baseline differences in severity of illness as the patients in Trial I were rated to be initially rather more than less ill compared to those in the other trials. In Trials I and III the percentage of patients with marked or moderate improvements compared to baseline was obviously larger in the silexan group than in the placebo group. In Trial II silexan showed a slight advantage in clinical global impressions improvement over lorazepam.

Tab. 4: Incidence of adverse events (AEs)

Trial	N	Patients with AE	Events	Events per day of exposure
Silexan				
I	104	39 (37.5%)	55	0.008
II	40	20 (50.0%)	26	0.012
III	86	29 (33.7%)	34	0.006
IV	50	25 (50.0%)	37	0.020
Placebo				
I	108	35 (32.4%)	68	0.009
III	84	30 (35.1%)	36	0.006
Lorazepam				
II	37	18 (48.6%)	19	0.009

Clinical safety and tolerability

The incidence of adverse events under silexan and comparators is presented in Tab 4. In the reference controlled or open-label studies II and IV the adverse event rates under silexan were slightly higher than in the placebo-controlled studies I and III. In the latter two trials the incidence rate and density of adverse events in the silexan group were comparable to those in the placebo group.

The only adverse events that occurred under silexan with a notably higher rate than under placebo or lorazepam were eructation (silexan: Trial I 3.7%, Trial II 7.5%, Trial III 7.0%, Trial IV 16.0%; placebo 0.0%; lorazepam 0.0%) and dyspepsia (silexan: Trial I 4.7%, Trial II 5.0%, Trial III 0.0%, Trial IV 0.0%; placebo 1.6%; lorazepam 0.0%).

Discussion

Subthreshold anxiety disorder is a serious, often unrecognized or unnoticed, and therefore undertreated condition that is nevertheless associated with a high degree of comorbidity and suffering [8, 11–13]. It has a low rate of spontaneous remission, may seriously interfere with important activities of daily living, and may evolve into a more chronic form of anxiety like GAD if not adequately treated [11–16]. As undertreatment may partly result from the reluctance of patients and physicians to administer medicinal products with potentially disturbing or even disabling side effects in a subthreshold, albeit nevertheless serious disorder, it is important to develop treatment options that effectively reduce anxiety without causing side effects which may undermine the therapeutic rationale that has led to their prescription.

Although subthreshold anxiety, or anxiety disorder NOS according to DSM-IV criteria, is a quite common condition [2–5], and several recommendations for its treatment have been published [16, 33, 34], it was surprising to note that a Medline search performed by the authors revealed only one interventional study in which the efficacy of a treatment was investigated in this condition – the study reported by Kasper and colleagues [23] which has been included into this review as Trial I.

Kasper et al.'s results demonstrate that silexan, at a dose of 80 mg/day, is both efficacious and safe in anxiety disorder NOS. The herbal medicinal product had a meaningful anxiolytic effect and alleviated anxiety related disturbances of sleep while improving physical and mental well-being. Silexan demonstrated an advantage of at least 4 points (lower bound of confidence interval for difference in means) over placebo in HAMA total score reduction after 10 weeks, but showed a clinically detectable treatment effect already after two weeks. It is also worth mentioning that about half of the patients treated with silexan (compared to 19.4% in the placebo group) did not show any signs of mental illness or presented with only borderline residual pathology at treatment end.

These results are fully supported by those of Woelk and colleagues [24] in patients with syndromal GAD. In this population silexan had a similar anxiolytic effect during the 6-week randomized treatment period as in the same period of the trial reported by Kasper et al. At the same time Woelk and colleagues were able to demonstrate that the anxiolytic effect of silexan in GAD was comparable to that of lorazepam, one of the most frequently prescribed benzodiazepines.

Volz and colleagues [6] have observed that on the foundations of evidence based medicine no therapeutic recommendations for subthreshold anxiety could be given as, at the time of publishing their paper, no interventional trials in this indication had been published. Indeed, clinical experience from other anxiety disorders, e.g. GAD, may not be readily transferable to subthreshold anxiety disorder and vice versa without further investigation. In this context the study of Kasper and colleagues [23] can be regarded as a first step towards an evidence based treatment recommendation for subthreshold GAD.

The studies on restlessness/agitation [25] and on neurasthenia, posttraumatic stress disorder and somatization disorder [27] included into this review of the clinical efficacy of silexan suggest that the herbal essence may be beneficial to the patient also in conditions where comorbidity factors like restlessness are more

important than excessive worries or anxious mood. Both trials show that silexan was effective in reducing the patients' anxiety levels that were underlying the direct symptoms defining the applied diagnostic categories. They also indicate a beneficial and clinically meaningful effect of the medicinal product on restlessness in particular. Trial III confirms the results of trial I regarding HAMA-A total score reduction and response. Trial IV was an exploratory study that was intended for describing the drug's effects in symptoms associated with neurasthenia and PTSD.

The incidence of adverse events in patients treated with silexan 80 mg/day was on a comparable level with placebo. It is noteworthy that the trials included into the review did not indicate any specific adverse reactions except gastrointestinal symptoms such as eructation or dyspeptic complaints. These findings are supported by toxicology studies in man which also did not reveal other specific adverse reactions to silexan at doses up to 8-fold of the recommended therapeutic dose after single administration and up to 4-fold of the therapeutic dose in subjects on a steady state. The observation that the adverse event rates for silexan in the non-controlled, open-label trial and in the trial against lorazepam were slightly higher than in those against placebo may be attributable to the fact that in these studies patients and physicians were aware that all participants were receiving a pharmacologically active compound. This may in turn have influenced their expectations and reporting practices.

In conclusion, the novel, oral lavender oil preparation silexan, administered once daily at a dose of 80 mg/day, was superior to placebo in patients suffering from anxiety disorder. In GAD the medicinal product was comparably efficacious as lorazepam. In addition to its anxiolytic effect silexan also improved associated symptoms such as restlessness, disturbed sleep and somatic complaints, and had a beneficial influence on general well-being and quality of life. The studies reviewed did not indicate any specific adverse reactions to silexan other than more or less trivial gastrointestinal complaints that may be unpleasant but not disabling or serious. Silexan showed no unwanted sedative effects, has no potential for drug abuse and causes no hangover effects.

With only one published interventional trial to date in subthreshold GAD further research on the efficacy of silexan and other medicinal products in this indication would be highly welcome to substantiate an evidence based treatment recommendation. The data indicate, however, that silexan could be a promising and well-tolerated option for these patients.

Conflict of interest

Prof. Dr. 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, Sepracor, Servier, Pierre Fabre, and Janssen.

Prof. 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.

Prof. 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.

Prof. 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.

Prof. 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.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. American Psychiatric Association, Washington, DC, 1994.
[2] Carter RM, Wittchen HU, Pfister H, et al. One-year prevalence of subthreshold and threshold DSM-IV generalized anxiety disorder in a nationally representative sample. Depress Anxiety, 13: 78–88, 2001.
[3] Cohen CI, Magai C, Yaffee R, et al. The prevalence of anxiety and associated factors in a multiracial sample of older adults. Psychiatr Serv, 57: 1719–1725, 2006.
[4] Heun R, Papassotiropoulos A, Ptok U. Subthreshold depressive and anxiety disorders in the elderly. Eur Psychiatry, 15: 173–182, 2000.
[5] Wittchen HU, Kessler RC, Beesdo K, et al. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry, 63(Suppl 8): 24–34, 2002.
[6] Volz HP, Gastpar M, Kasper S, et al. Subsyndromale Angststörungen: Definition, Messparameter, Epidemiologie. Neurol Neurochir Psychiatr, 10(Pre-Publishing Online): 1–6, 2009.

[7] Lawrence AE, Brown TA. Differentiating generalized anxiety disorder from anxiety disorder not otherwise specified. J Nerv Ment Dis, 197: 879–886, 2009.
[8] Kessler RC, Brandenburg N, Lane M, et al. Rethinking the duration requirement for generalized anxiety disorder: evidence from the National Comorbidity Survey Replication. Psychol Med, 35: 1073–1082, 2005.
[9] Ruscio AM, Chiu WT, Roy-Byrne P, et al. Broadening the definition of generalized anxiety disorder: effects on prevalence and associations with other disorders in the National Comorbidity Survey Replication. J Anxiety Disord, 21: 662–676, 2007.
[10] Pincus HA, Davis WW, McQueen LE. 'Subthreshold' mental disorders. A review and synthesis of studies on minor depression and other 'brand names'. Br J Psychiatry, 174: 288–296, 1999.
[11] Lewinsohn PM, Shankman SA, Gau JM, et al. The prevalence and comorbidity of subthreshold psychiatric conditions. Psychol Med, 34: 613–622, 2004.
[12] Yonkers KA, Dyck IR, Warshaw M, et al. Factors predicting the clinical course of generalised anxiety disorder. Br J Psychiatry, 176: 544–5449, 2000.
[13] Wittchen HU, Carter RM, Pfister H, et al. Disabilities and quality of life in pure and comorbid generalized anxiety disorder and major depression in a national survey. Int Clin Psychopharmacol, 15: 319–328, 2000.
[14] Aune T, Stiles TC. Universal-based prevention of syndromal and subsyndromal social anxiety: A randomized controlled study. J Consult Clin Psychol, 77: 867–879, 2009.
[15] Diefenbach GJ, Hopko DR, Feigon S, et al. 'Minor GAD': characteristics of subsyndromal GAD in older adults. Behav Res Ther, 41: 481–487, 2003.
[16] Rickels K, Schweizer E. The spectrum of generalised anxiety in clinical practice: the role of short-term, intermittent treatment. Br J Psychiatry Suppl, 34: 49–54, 1998.
[17] Lader MH. Limitations on the use of benzodiazepines in anxiety and insomnia: are they justified? Eur Neuropsychopharmacol, 9(Suppl 6): S399–S405, 1999.
[18] Longo LP, Johnson B. Addiction: Part I. Benzodiazepines – side effects, abuse risk and alternatives. Am Fam Physician, 61: 2121–2128, 2000.
[19] Westenberg HG, Sandner C. Tolerability and safety of fluvoxamine and other antidepressants. Int J Clin Pract, 60: 482–491, 2006.
[20] European Directorate for the Quality of Medicines an Healthcare. Lavender oil (Lavandulae aetheroleum). In: European, 5th edn. Strasbourg, France. European Directorate for Quality of Medicines and Healthcare (EDQM), pp. 1894–1895, 2005.
[21] Cavanagh HM, Wilkinson JM. Biological activities of lavender essential oil. Phytother Res, 16: 301–308, 2002.
[22] Elizabetsky E, Marschner J, Souza DO. Effects of linalool on glutamatergic system in the rat cerebral cortex. Neurochem Res, 20: 461–465, 1995.
[23] Kasper S, Gastpar M, Müller WE, et al. Silexan, an orally administered Lavandula oil preparation, is effective in the treatment of 'subsyndromal' anxiety disorder: a randomized, double-blind, placebo controlled trial. Int Clin Psychopharmacol, 25: 277–287, 2010.
[24] Woelk H, Schläfke S. A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder. Phytomedicine, 17: 94–99, 2010.
[25] Kasper S, Anghelescu I, Dienel A. Efficacy of Silexan (WS® 1265) in Patients with Restlessness and Sleep Disturbance. In: Annual Congress of the German Society for Psychiatry and Psychotherapy (DGPPN). Berlin, Germany; 2010.
[26] Uehleke B, Schaper S, Dienel A, et al. Phase II trial on the effects of Silexan in patients with neurasthenia, posttraumatic stress disorder or somatization disorder. Submitted for publication.
[27] Stange R, Schaper S, Uehleke B, et al. Phase II study on the effects of lavender oil (Silexan) in patients with neurasthenia, post-traumatic stress disorders or somatisation disorder (Abstract). Focus Alter Complementary Therapies, 12: 46, 2007.
[28] Zung WW. A rating instrument for anxiety disorders. Psychosomatics, 12: 371–379, 1971.
[29] Kendall PC, Finch AJ Jr, Auerbach SM, et al. The State-Trait Anxiety Inventory: a systematic evaluation. J Consult Clin Psychol, 44: 406–412, 1976.
[30] Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res, 28: 193–213, 1989.
[31] Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care, 30: 473–483, 1992.
[32] National Institute of Mental Health. 12 – CGI. Clinical Global Impressions. In: Guy W, (ed) EDCEU assessment in psychopharmacology. U.S. National Institute of Mental Health, Psychopharmacology Research Branch, Rockville, MD, pp. 217–222, 1970.
[33] Helmchen H. Unterschwellige psychische Störungen. Nervenarzt, 72: 181–189, 2001.
[34] Helmchen H, Linden M. Subthreshold disorders in psychiatry: clinical reality, methodological artifact, and the double-threshold problem. Compr Psychiatry, 41: 1–7, 2000.