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REVIEW ARTICLE

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An orally administered lavandula oil preparation (Silexan) for anxiety disorder and related conditions: an evidence based review

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Abstract
Objective. Silexan is a lavender oil preparation in gelatine capsules containing 80 mg. We reviewed the clinical trials investigating the anxiolytic efficacy and tolerability of Silexan as well as its safety and potential for drug interactions. *Methods*. Seven trials were included, among which four therapeutic trials had a treatment duration of 6 or 10 weeks. *Results*. In patients with subsyndromal anxiety or generalised anxiety disorder (GAD) an anxiolytic effect of Silexan was evident after 2 weeks. Patients treated with Silexan showed Hamilton Anxiety Scale (HAMA) total score decreases between 10.4 ± 7.1 and 12.0 ± 7.2 points at Week 6 and between 11.8 ± 7.7 and 16.0 ± 8.3 points at Week 10. *Conclusions*. HAMA total score reductions between baseline and end of treatment were significantly superior to placebo in patients with subsyndromal anxiety and comparable to lorazepam in its starting dose in patients with GAD. Silexan had beneficial effects on typical co-morbidity symptoms of anxiety disorders, for example, disturbed sleep, somatic complaints, or decreased quality of life. Except for mild gastrointestinal symptoms, the drug was devoid of adverse effects and did not cause drug interactions or withdrawal symptoms at daily doses of 80 or 160 mg.

Key words: Silexan, lavender oil, anxiety disorder, review, clinical trials, efficacy

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Introduction

According to a recent study, the three most prevalent mental disorders in the European Union are anxiety disorders, insomnia, and major depression, with 12-month prevalence rates of 14%, 7%, and 6.9%, respectively (Wittchen et al. 2011). Anxiety disorder is thus by far the most prevalent psychiatric illness in Western Europe. There is evidence that the true percentage of patients who suffer from pathological symptoms of anxiety may even exceed 20% (Wittchen et al. 2002) when patients with subsyndromal manifestations of anxiety who meet some, but not all of the criteria for anxiety disorders required according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) are included (Volz et al. 2009). Subsyndromal presentations of anxiety disorder in particular are sometimes not easily recognised in clinical practice although they are associated with a similar degree of functional impairment, distress and risk of co-morbidity as syndromal presentations (Kessler et al. 2005; Lewinsohn et al. 2004; Pincus et al. 1999). It is thus not surprising that, according to a recent mental health survey, more than half of the patients affected by anxiety disorders do not receive appropriate treatment (Andrews and Carter 2001).

In addition to benzodiazepines that have been used as first-line treatment for anxiety disorders for decades, currently available pharmacological treatment options include antidepressants (notably selective serotonin reuptake inhibitors, SSRIs), buspirone, propranolol, hydroxyzine and gabapentin. While the side effects of benzodiazepines include sedation, attention problems, amnesia, depression, delirium, dependence and withdrawal syndrome (Lader 1999; Longo and Johnson 2000), more recently developed drugs with anxiolytic properties often have more favourable tolerability profiles but may still cause disturbing unwanted effects that may interfere with essential activities of daily living. This may contribute to the under-treatment of anxiety disorders. A well-tolerated anxiolytic drug could thus dissipate the reservations of those concerned and could lay the foundations for better treatment acceptance and compliance.

Lavender *(Lavandula angustifolia)* has been known for centuries as a medicinal plant. It has been ascribed anxiolytic as well as calming properties (Cavanagh and Wilkinson 2002), and as such it is justified to investigate the efficacy of this herbal drug as an anxiolytic agent. As an oil derived from the flowers of the plant by steam distillation, the herbal essence is a complex, multi-ingredient mixture in which more than 160 different substances have been identified. The anxiolytic properties of the drug have been ascribed to different ingredients [among them linalool and linalyl acetate (Setzer 2009)]. According to *in vitro* studies, lavender oil exerts effects on the $GABA_A$ receptor and inhibits the presynaptic calcium channels (Aoshima and Hamamoto 1999). In man the effect of the essential oil has been investigated to date always as a whole (Cavanagh and Wilkinson 2002).

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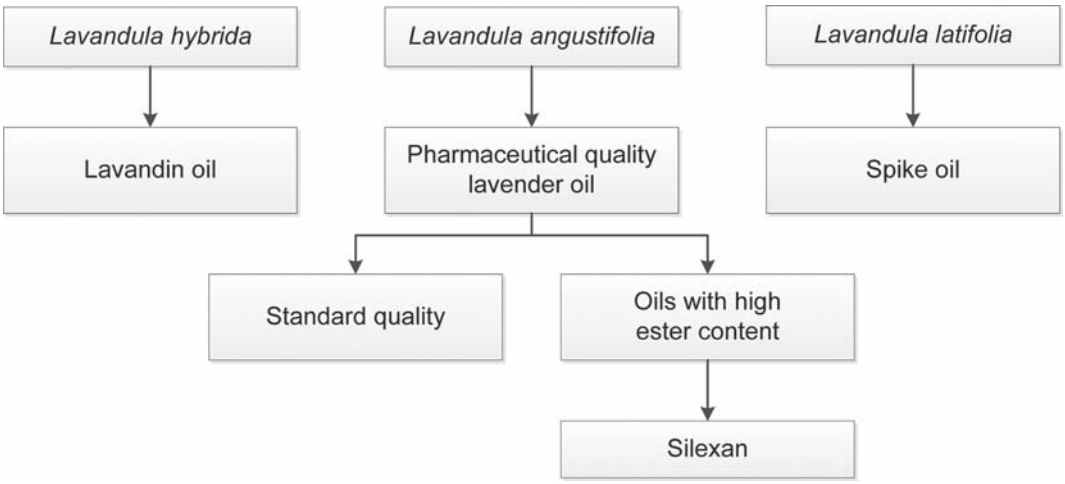

Figure 1. Lavender oils with pharmaceutical and non-pharmaceutical quality.

The suitability of lavender oils for the manufacturing of medicinal products, and also their market value, is mainly determined by their linalyl acetate content. Apart from high-ester oil from *Lavandula angustifolia* that is used primarily for pharmaceutical quality preparations, lower quality oils from this plant as well as oils from other subspecies of lavender are available for other uses, for example, for manufacturing fragrances, perfumes and body care products, or as solvents (Figure 1). Marketed oils from lavender thus differ greatly with regard to quality and manufacturing cost. It is therefore not surprising that an investigation performed by Binder and König found impurities caused by the admixture of lavandin oil or synthetic substances in 9 out of 22 allegedly pharmaceutical-quality lavender oil products obtained from pharmacies and retailers (2000).

Silexan[1] is a preparation from *Lavandula angustifolia* for oral use. The manufacturing process is well-defined to assure invariant ingredients with particularly high ester content and low cineol content. In Germany, the drug is registered as a medicinal product for the treatment of restlessness related to anxious mood.

We reviewed the results of clinical trials investigating the efficacy and tolerability of Silexan in anxiety disorder and related conditions and reported the results of interaction studies as well as of an investigation of potential withdrawal effects.

Material and methods

Study/patient characteristics

Our review includes all clinical trials involving Silexan that were published by September 2012. A total of seven trials were identified.

Our review of the efficacy of Silexan in anxiety disorder and related conditions is based primarily on three double-blind, randomised, controlled, multicentre trials of clinical phase III. Study A (Kasper et al. 2010c) investigated the efficacy of the herbal drug in comparison to placebo in patients suffering from subsyndromal anxiety disorder (classified as 'anxiety disorder not otherwise specified' according to the DSMIV criteria) while Study B compared Silexan and the benzodiazepine lorazepam in its starting dose in patients with generalised anxiety disorder (GAD) (Woelk and Schläfke 2010). The participants of Study C that compared Silexan to placebo were suffering from restlessness and agitation (Kasper et al. 2010a). Furthermore, preliminary evidence on the efficacy of Silexan in neurasthenia, posttraumatic stress disorder and somatisation disorder was derived from Study D that was performed as an open-label, uncontrolled phase II trial (Uehleke et al. 2012). The main characteristics of Studies A through D are shown in Table I.

Three additional trials were included into our review for further insight into the safety and tolerability of Silexan (Table II). Studies E and F were single-centre, double-blind, randomised, placebo-controlled crossover trials in healthy volunteers that investigated a potential influence of the herbal drug on human cytochrome P450 (CYP) activity (Study E) and on the contraceptive efficacy of Microgynon®, a combined oral contraceptive whose active compounds are ethinylestradiol and levonorgestrel (Study F) (Kasper and Dienel 2011). Study G was a four-arm double-blind, randomised, controlled, multicentre trial of clinical phase III that included patients suffering from GAD, and in which two different doses of Silexan were compared to placebo and to paroxetine (Kasper et al. 2011). Although the main results of the study have not been published yet, we include the results from a withdrawal investigation that was performed in the context of the trial.

Interventions

Silexan is a defined preparation from *Lavandula angustifolia* Mill. derived from the fresh flowers of the plant by steam distillation. The product is available in immediate release soft gelatine capsules containing 80 mg of lavender oil. According to the German marketing authorisation the recommended dose is 1×80 mg/day. In the therapeutic studies A–D and G the duration of treatment with Silexan was 6 or 10 weeks.

[1]Silexan (R) is an active substance manufactured by Dr. Willmar Schwabe GmbH & Co. KG.

Table I. Main characteristics of studies investigating therapeutic efficacy.

Trial	A (Kasper et al. 2010c)	B (Woelk and Schläfke 2010)	C (Kasper et al. 2010a)	D (Uehleke et al. 2012)
Design characteristics	Double-blind, randomized, placebo-controlled multicentre trial	Double-blind, double-dummy, randomized, reference-controlled multicentre trial	Double-blind, randomized, placebo-controlled multicentre trial	Open, non-comparative, single-centre pilot study
Diagnosis for inclusion	Anxiety disorder not otherwise specified (DSMIV 300.00; ICD-10 F41.9)	Generalised anxiety disorder (DSMIV 300.02)	Restlessness and agitation (ICD10 R45.1)	Neurasthenia (ICD10 F48.0), posttraumatic stress disorder (F43.1), or somatization disorder (F45.0, F45.1)
Interventions, no. of patients evaluated for efficacy	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
Primary efficacy outcome measures	Hamilton Anxiety Scale (HAMA); Pittsburgh Sleep Quality Index (PSQI)	Hamilton Anxiety Scale (HAMA)	Hamilton Anxiety Scale (HAMA); Pittsburgh Sleep Quality Index (PSQI)	State Check; State-Trait Anxiety Inventory (STAI); sleep diary; Symptom Checklist (SCL90R); SF-36 Health Survey Questionnaire
Main secondary efficacy outcome measures	Zung Self-rating Anxiety Scale (SAS); SF-36 Health Survey Questionnaire; Clinical Global Impressions (CGI)	Zung Self-rating Anxiety Scale (SAS); sleep diary; SF-36 Health Survey Questionnaire; Clinical Global Impressions (CGI)	Zung Self-rating Anxiety Scale (SAS); State Check; Clinical Global Impressions (CGI)	

Main outcome measures

Studies A through C used the total score change of the Hamilton Anxiety Scale (HAMA, Hamilton 1976) between baseline and the end of randomised treatment as the primary outcome measure for efficacy. The investigators' assessment of anxiety using the HAMA was complemented by the patient-rated Zung Self-rating Anxiety Scale (SAS, Zung 1971). In Study D the State-Trait Anxiety Inventory (STAI, Kendall et al. 1976) was used as a self-report measure of anxiety. Sleep quality was either assessed by the Pittsburgh Sleep Quality Index (PSQI, Buysse et al. 1989), which was used as a co-primary endpoint in Studies A and C, or by means of a sleep diary. Other efficacy outcome measures used in three out of these four trials included the SF-36 Health Survey Questionnaire (Ware and Sherbourne 1992) that assesses a broad spectrum of general health concepts (limitations in physical activities due 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

Table II. Main characteristics of studies investigating safety measures.

Trial	E (Kasper and Dienel 2011)	F (Kasper and Dienel 2011)	G (Kasper et al. 2011)
Assessment of	Drug interactions	Interaction with oral contraception	Withdrawal symptoms
Design characteristics	Single-centre, double-blind, randomised, placebo-controlled crossover study	Single-centre, double-blind, randomised, placebo-controlled crossover study	Double-blind, double-dummy, randomized, reference-controlled multicentre trial
Participants	Healthy male or female volunteers	Healthy female volunteers	Patients with generalised anxiety disorder (DSMIV 300.02)
Interventions, number of subjects evaluated for safety	1 × 160 mg/day Silexan or placebo for 10 days, 21 days wash-out ($n = 16$)	1 × 160 mg/day Silexan or placebo for 28 days ($n = 24$) Oral contraception: 0.15 mg levonorgestrel + 0.03 mg ethinylestradiol/day	1 × 160 mg/day Silexan ($n = 97$), 1 × 80 mg/day Silexan ($n = 115$) or placebo ($n = 105$), 10 weeks
Main safety outcome measures	Probe substrates: CYP 1A2 caffeine (150 mg), CYP 2C9 tolbutamide (125 mg), CYP 2C19 omeprazole (20 mg), CYP 2D6 dextrometorphan (30 mg), CYP 3A4 midazolam (2 mg) AUC_{0-t} in plasma; genotyping for CYP2C19 and CYP2D6	Ethinylestradiol and levonorgestrel pharmacokinetics (Days 1 and 28), follicle size (Days 7, 14, 21 and 28), plasma concentration of progesterone, estradiol (Days 7, 14, 21 and 28) and sex hormone-binding globulin (SHBG) (Day 21); Hoogland score	Physician Withdrawal Checklist (PWC-20) administered at treatment end and 1 week thereafter

pain; general mental health; vitality; general health perceptions) with implications on activities of daily living and quality of life, and the Clinical Global Impressions scale (CGI, National Institute of Mental Health 1970), an observer-rated summary measure for the (change in) severity of mental illness. The State Check inventory used in Trials C and D was an unpublished compilation of one-item measures assessing the severity and the extent of change of several direct symptoms of GAD. Due to its exploratory concept the investigators in Study D made no distinction between primary and secondary outcome measures.

In all trials tolerability and safety were primarily assessed by monitoring adverse events. Drug interactions of Silexan were assessed in Studies E and F by monitoring the pharmacokinetic parameters of several phenotyping compounds (Study E) or of ethinylestradiol and levonorgestrel (Study F). In Study F the subjects' ovulation status was assessed using the Hoogland Score (Hoogland and Skouby 1993). In study G the Physician Withdrawal Checklist (PWC-20, Rickels et al. 2008), that was originally developed to detect benzodiazepine-like withdrawal symptoms caused by anxiolytics of the non-SSRI type, was evaluated at the end of the 10-week randomised treatment period as well as 1 week thereafter.

Ethics

All primary trials included into this review were performed under consideration of the principles of Good Clinical Practice and the Declaration of Helsinki. Independent ethics committees approved the protocols and their submitted appendices.

Statistics

Studies A and C were performed with the intention of demonstrating superiority of Silexan over placebo whereas Study B was a trial that used lorazepam as an active control. Study D was an exploratory trial in which no primary outcome measure had been pre-specified. Results for baseline data, change from baseline and responder rates were adopted from the primary publications. All studies used a last observation carried forward approach for imputing missing efficacy data.

In responder analyses patients who presented with a HAMA total score reduction between baseline and end of treatment by at least 50% of the baseline value were considered responders (in Trial A responders had to present with a 50% reduction of the HAMA total score or of the PSQI total score).

Results

Study participants

Table III shows the baseline characteristics of the patients included into Trials A through D. In Trial D 57.5% of the 47 participants suffered from neurasthenia, 63.9% had post-traumatic stress syndrome and 19.1% were diagnosed to have somatization disorder (multiple responses). In Trials A through D only minor baseline treatment group differences were observed for basic demographic data as well as for baseline efficacy outcome measures.

The participants of the interaction Study E were 16 healthy volunteers 8 of whom were female. Twenty-four healthy women of childbearing potential were included into the contraceptives interaction Study F. In Trial G, the first PWC assessment performed at treatment end served as the baseline for withdrawal symptoms. The mean (± SD) PWC20 total scores were 6.7 ± 9.7 points for Silexan 160 mg/day, 7.5 ± 7.4 points for Silexan 80 mg/day and 11.4 ± 10.8 points in the placebo group. The authors of the primary publication attributed the baseline differences between Silexan and placebo to the fact that the PWC20 includes withdrawal symptoms like anxiety, nervousness and restlessness or agitation that are reduced by Silexan.

Efficacy

A detailed review of the efficacy data of Studies A through D has been presented by Kasper et al. (2010b). The results for the main efficacy outcome measures are shown in Table IV.

Regarding the anxiolytic effect of the investigational treatment Silexan was significantly superior to placebo according to the investigators' rating (HAMA) as well as to the patients' self-rating (Zung SAS) in Trial A. In this trial, statistically significant differences to placebo were observed during all HAMA assessments performed at 2, 4, 6, 8 and

Table III. Trials A–D: baseline characteristics (full analysis set; patients (%), or mean ± SD).

Trial	A		B		C		D
Treatment	Silexan	Placebo	Silexan	Lorazepam	Silexan	Placebo	Silexan
N	104	108	40	37	86	84	47
Sex: female patients	76 (73.1%)	83 (76.9%)	33 (82.5)	26 (70.3)	62 (72.1%)	60 (71.4%	39 (83.0%)
Age (years)	46 ± 11	47 ± 11	49 ± 11	46 ± 13	48 ± 11	47 ± 13	52 ± 9
HAMA total score	26.8 ± 5.4	27.1 ± 5.3	24.9 ± 3.7	24.7 ± 3.7	25.5 ± 6.0	26.5 ± 6.1	n/a
PSQI total score	12.3 ± 2.9	12.6 ± 3.0	n/a	n/a	12.2 ± 2.5	12.7 ± 2.8	n/a
Zung SAS total score	60.1 ± 9.9	61.1 ± 10.1	61.4 ± 6.6	61.5 ± 5.5	54.5 ± 12.3	55.9 ± 10.3	n/a
SF-36 mental health	32.3 ± 17.4	32.6 ± 21.2	39.9 ± 15.9	36.5 ± 13.0	n/a	n/a	39.0 ± 15.5
CGI item 1 – markedly or severely ill	62 (59.6%)	73 (67.6%)	20 (50.0%)	19 (51.4%)	49 (57.0%)	46 (54.8%)	n/a
STAI, State Anxiety	n/a	n/a	n/a	n/a	n/a	n/a	46.2 ± 10.8
STAI, Trait Anxiety	n/a	n/a	n/a	n/a	n/a	n/a	53.9 ± 7.8

n/a, not assessed.

Table IV. Trials A–D: outcome measures – change between baseline and end of treatment (full analysis set; mean ± SD or patients (%); last observation carried forward).

Trial	A		B		C		D
Treatment	Silexan	Placebo	Silexan	Lorazepam	Silexan	Placebo	Silexan
N	104	108	40	37	86	84	47
HAMA total score[#]	−16.0 ± 8.3*	−9.5 ± 9.1	−11.3 ± 6.7	−11.6 ± 6.6	−11.8 ± 7.7*	−9.6 ± 8.7	n/a
Responder HAMA ≥ 50%-Reduction	76.9%*	49.1%	52.5%	40.5%	48.8%*	33.3%	n/a
PSQI total score[#]	−5.5 ± 4.4*	−3.8 ± 4.1	n/a	n/a	−4.8 ± 4.0	−4.3 ± 4.5	n/a
Zung SAS total score[#]	−15.6 ± 11.4*	−11.1 ± 12.2	−14.8 ± 11.4	−14.4 ± 8.5	−11.2 ± 10.1	−9.3 ± 10.4	n/a
SF-36 physical health[§]	20.5 ± 22.6*	10.8 ± 19.8	12.5 ± 17.4	16.9 ± 18.0	n/a	n/a	8.3 ± 16.6
SF-36 mental health[§]	32.5 ± 24.1*	19.8 ± 22.4	21.2 ± 18.6	24.3 ± 18.7	n/a	n/a	18.8 ± 22.3
CGI item 1 – not at all ill/ borderline mentally ill	51 (49.0%)*	21 (19.4%)	3 (7.5%)	3 (8.1%)	17 (19.8%)*	12 (14.3%)	n/a
CGI item 2 – marked/ moderate improvement	77 (74.0%)*	44 (40.7%)	28 (70.0%)	19 (51.4%)	45 (52.3%)*	27 (32.1%)	n/a
STAI, State Anxiety[#]	n/a	n/a	n/a	n/a	n/a	n/a	−4.5 ± 10.7
STAI, Trait Anxiety[#]	n/a	n/a	n/a	n/a	n/a	n/a	−7.4 ± 8.9

n/a, not assessed.
*Difference to placebo: $p < 0.05$ (CGI: p value for original uncategorized distribution).
[§]Positive differences denote improvement.
[#]Negative differences denote improvement.

10 weeks after baseline as well as for the Zung SAS which was only administered at baseline and treatment end. In Trial C, symptoms of anxiety were reduced more obviously in patients treated with Silexan than in the placebo group. This holds true for investigator ratings as well as for the patients self-rating. In Trial B, Silexan and lorazepam showed comparable reductions of anxiety levels for both observer and self-rating. At treatment end average anxiety score improvement was generally more pronounced in Trial A as compared to that of Trial B; however, this was confounded with different durations of randomised treatment (10 weeks in Trial A and 6 weeks in Trial B), and at the end of Week 6 the patients treated with Silexan in Trial A showed comparable improvements to those in Trial B when average HAMA total score decreases between 10.4 ± 7.1 and 12.0 ± 7.2 points were observed for the herbal essence. After 10 weeks of treatment the responder rates were 76.9% for silexan and 49.1% for placebo ($p \leq 0.01$) in Trial A, and 48.4% and 33.3% in Trial C ($p \leq 0.05$). In Trial B responder rates of 52.5% and of 40.5% were determined for Silexan and lorazepam, respectively (difference in favour of Silexan: 12.0%; 90% confidence interval: −6.6%; 30.5%), after 6 weeks of treatment. After 6 weeks of treatment with Silexan in Trial D, which did not include a control group, the participants showed a reduction by 9.7% of the baseline mean score for state anxiety and by 13.7% for trait anxiety (change vs. baseline, both sub-scores: $p < 0.01$).

The effects of the treatments on sleep and restlessness were assessed using the PSQI, the State Check inventory as well as sleep diary data. According to the PSQI Silexan was significantly superior to placebo in improving the sleep quality of patients with subsyndromal anxiety (Trial A) but showed only minor advantages in patients with restlessness and agitation (Trial C). The assessment of sleep quality in Trials B and D was based on a sleep diary which the patients maintained on a daily basis. In Trial D total sleep time increased in comparison to baseline ($p = 0.08$), whereas bed time changed only marginally. The study also showed improvements regarding waking-up frequency and duration ($p < 0.01$) and sleep efficiency ($p = 0.04$), morning tiredness ($p = 0.01$) and mood ($p = 0.06$). In Trial B similar improvements of sleep diary measures were noted, none of which were significantly different between Silexan and lorazepam. In Trial C 86.1% of the 86 patients in the Silexan group and 90.5% of the 84 patients in the placebo group felt often or always restless at baseline. By the end of randomized treatment at Week 10 these rates decreased to 28.0% for Silexan and to 41.7% for placebo ($p \leq 0.01$).

According to the SF-36 Silexan significantly ameliorated the limitations of activities of daily living in patients with subsyndromal anxiety (Trial A), both in the mental and in the physical domain. In Trial B that included patients with GAD, the improvements from baseline under both Silexan and lorazepam were less pronounced, but again the different treatment durations (Trial A: 10 weeks; Trial B: 6 weeks) have to be taken into account. Table IV also shows that in Trial B patients treated with lorazepam showed somewhat more pronounced improvements of activities of daily living than those treated with Silexan.

In Trials A and C the percentage of patients whose mental condition was rated to be moderately or markedly improved in comparison to baseline according to Item 2 of the CGI was substantially larger in the Silexan group than in the placebo group, with rate differences of 33% and 20%, respectively. In Trial B the rate of moderately or markedly improved patients under Silexan was by a difference of 19% higher than for lorazepam.

Interaction studies

Trial E investigated a potential influence of Silexan co-administration on the activity of major CYP enzymes. The interaction potential was assessed using the ratio between the phenotyping metrics ($AUC_{0\text{-}t}$) for the plasma

concentrations of the phenotyping compounds after co-administration of Silexan and placebo. The Silexan/placebo ratios for AUC_{0-t} were close to unity for all CYPs. Repeated Silexan administration did not cause clinically relevant inhibitory or inducing effects on CYP1A2, CYP2C9, CYP 2C19, CYP2D6 and CYP3A4.

In Study F a pre-specified equivalence range of 0.80–1.25 for the ratio between the levels of ethinylestratiol or levonogestrel during co-administration of Silexan and placebo was used for determining equivalence. The 90% confidence interval for AUC_{0-t} fell within the acceptable range for both sex hormones, and this was also the case for C_{max}. These findings were supported by similar results for sex hormone-binding globulin (SHBG) obtained at Day 21 of each treatment period (mean ± SD: 113.5 ± 40.9 and 112.7 ± 40.0 nmol/l for co-administration of Silexan and placebo, respectively). A Hoogland score 3 points or more (indicating increased ovarian activity) and a follicle size greater than 13 mm were observed in one subject during the cycle with placebo co-administration but in none of the subjects during Silexan treatment.

Safety and tolerability

In the placebo-controlled 10-week trials A and C the percentage of patients with any adverse events under Silexan treatment were 36.4% and 33.7%, respectively, compared to 32.1% and 35.7% in the placebo group. In Trial B the percentages of patients with any events under Silexan or lorazepam were also comparable (50.0% and 48.6%, respectively).

Eructation-associated events (Silexan: Trial A 4.7%, Trial B 7.5%, Trial C 7.0%, Trial D 16.0%; placebo 0.0%; and lorazepam 0.0%) and dyspepsia (Silexan: Trial A 4.7%, Trial B 5.0%, Trial C 0.0%, Trial D 0.0%; placebo 1.6%; and lorazepam 0.0%) were the only adverse events that occurred under Silexan with a notably higher frequency than under placebo or lorazepam. In Trials E and F, which were performed in healthy volunteers, mild gastrointestinal complaints, mainly eructation, were the most frequent adverse events. In the placebo-controlled trials A, C and G the percentage of patients treated with Silexan or placebo who reported adverse symptoms such as tiredness or lethargy was always lower than 1%, whereas such events were observed in 16.2% of the patients who received lorazepam in Trial B (risk difference for Trial B: 16.2% in favour of Silexan; 95% confidence interval: [4%; 31.1%]).

In Trial G the PWC20 withdrawal symptoms questionnaire was filled in first at the end of the 10-week randomised treatment period, when the investigational drugs were discontinued. The checklist was completed again one week later to investigate the development of withdrawal symptoms. As already mentioned above, Table V shows marked, dose-dependent treatment group differences at Week 10 that were attributed to the fact that some of the items of the scale were confounded with the intensity of anxiety disorder and related co-morbidity, and thus these symptoms were reduced by the anxiolytic effect of Silexan. As regards change between Weeks 10 and 11, an average decrease, not an increase of the number and intensity of potentially withdrawal-related symptoms was observed in all treatment groups, with no systematic differences between the two doses of Silexan and placebo.

Conclusion

In a recently published paper Perry et al. (2012) present a systematic review of randomised trials investigating the efficacy or effectiveness of various lavender preparations with different pharmaceutical formulations and routes of administration in reducing anxiety and stress. Out of 15 trials that met the authors' selection criteria, 13 were criticised because of methodological issues that limited the extent to which the anxiolytic effect of lavender could be evaluated, and only 2, the trials investigating the efficacy of Silexan published by Kasper et al. (2010b) (Trial A) and by Woelk and Schläfke (2010) (Trial B), received a score of 4 points on the 5-point Jadad scale (Jadad et al. 1996). Perry and colleagues concluded that the evidence for an anxiolytic effect of orally administered lavender is promising but needs to be confirmed by more trials with acceptable methodology. The remaining five trials considered in our work were not included by Perry and colleagues, who assessed lavender preparations in general and not specifically Silexan, because the diagnosis for inclusion was not anxiety disorder but a related condition (Trials C and D), were not randomised and controlled (Trial D), did not investigate the anxiolytic efficacy of the drug (Trials E and F), or because they had not yet been published in a peer-reviewed journal (Trials E, F, and G).

We agree with Perry and colleagues in that the trials reported by Kasper et al. (2010b) and by Woelk and Schläfke (2010) confirm a promising anxiolytic effect of Silexan administered at a once-daily dose of 80 mg for 10 weeks in patients with syndromal or subsyndromal GAD. Both trials indicate a clinically meaningful, very well-comparable anxiolytic effect already after 2 weeks of

Table V. Trial G: Physician Withdrawal Checklist (PWC-20) – total score and number of symptoms with a non-zero score (mean ± SD).

		Placebo ($n = 105$)	Silexan 80 mg/day ($n = 115$)	Silexan 160 mg/day ($n = 97$)
Total score	Week 10	11.4 ± 10.8	7.5 ± 7.4	6.7 ± 9.7
	Difference Week 11 – Week 10[#]	−0.2 ± 4.2	−0.2 ± 3.8	−0.7 ± 4.9
Number of symptoms	Week 10	7.6 ± 5.6	5.6 ± 4.3	4.7 ± 5.2
	Difference Week 11 – Week 10[#]	−0.3 ± 2.5	−0.4 ± 2.6	−0.3 ± 2.8

[#]Negative differences denote improvement.

treatment as well as a beneficial influence on general mental and physical health, and thus ultimately on quality of life. Both studies also demonstrate a beneficial effect of Silexan on disturbed sleep that was significantly superior to that of placebo and comparable to that of lorazepam in its starting dose, a drug that is also used in clinical practice for treating sleep disorders.

The studies in restlessness/agitation and disturbed sleep (Kasper et al. 2010a) as well as in neurasthenia, posttraumatic stress disorder and somatization disorder (Uehleke et al. 2012) included into this review complement this evidence by showing that Silexan has a meaningful therapeutic effect on important co-morbidities of anxiety disorders, or in conditions where co-morbidity factors like restlessness are more important than excessive worries or anxious mood.

Synthetic anxiolytic drugs, notably benzodiazepines, have been associated with unwanted sedative, addictive and withdrawal effects (Buffett-Jerrott and Stewart 2002; Iguchi et al. 1993; Onyett 1989; Petursson 1994). Our review shows that there are no sedative effects in patients treated with Silexan which was contrary to those exposed to lorazepam. Thus, unlike benzodiazepines, Silexan was therefore not associated with sedative effects that could interfere with important activities of daily living, for example, with operating machinery or with driving, while providing comparable anxiety relief and improvement of sleep. After up to 10 weeks of treatment Silexan was also devoid of symptoms of addiction or withdrawal. The results indicate that the drug can be discontinued without a need for down-titration.

The interaction studies included into our review demonstrated that Silexan is neither an inhibitor nor an inducer of the cytochrome P450 enzyme system that is important for the metabolism of the majority of currently marketed drugs. Furthermore, Silexan also does not modify the plasma levels of oral contraceptives based on ethinylestradiol or levonogestrel. The herbal essence can therefore be used safely in co-administration with the majority of other therapeutic agents and oral hormonal contraceptives.

In conclusion, the oral lavender oil preparation Silexan was superior to placebo in patients suffering from subsyndromal anxiety disorder and as efficacious as lorazepam in its starting dose in patients with syndromal GAD. The trials included into the review also suggest beneficial effects on co-morbidity symptoms like restlessness, disturbed sleep and somatic complaints, as well as a beneficial influence on general well-being and quality of life. Except for mild gastrointestinal symptoms, mainly eructation, the drug was devoid of adverse effects and did not cause drug interactions or withdrawal symptoms at daily doses of 80 or 160 mg.

Key points

- In sub-threshold anxiety disorder Silexan is superior to placebo. In GAD the drug was comparably efficacious as lorazepam in its starting dose.
- In addition to its anxiolytic properties Silexan has a beneficial effect on typical co-morbidity symptoms associated with anxiety disorders, for example, disturbed sleep, somatic complaints or decreased quality of life.
- Silexan is not sedating and has no interaction potential. As the drug does not cause withdrawal effects it can be discontinued without down titration.
- Adverse effects were limited to mild gastrointestinal events and were otherwise on one level with placebo.

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References

Andrews G, Carter GL. 2001. What people say about their general practitioners' treatment of anxiety and depression. Med J Aust 175:S48–S51.

Aoshima H, Hamamoto K. 1999. Potentiation of GABAA receptors expressed in Xenopus oocytes by perfume and phytoncid. Biosci Biotechnol Biochem 63:743–748.

Binder G, König WA. 2000. Ätherische Öle – Untersuchung zur Deklaration und Qualität ausgewählter Präparate. Deutsche Apotheker Zeitung 140:4205–4210.

Buffett-Jerrott SE, Stewart SH. 2002. Cognitive and sedative effects of benzodiazepine use. Curr Pharm Des 8:45–58.

Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213.

Cavanagh HM, Wilkinson JM. 2002. Biological activities of lavender essential oil. Phytother Res 16:301–308.

Hamilton M. 1976. Hamilton Anxiety Scale (HAMA). In: Guy W, editor. ECDEU assessment manual for psychopharmacology. Rockville, MD: U.S. National Institute of Health, Psychopharmacology Research Branch, pp. 193–197.

Hoogland HJ, Skouby SO. 1993. Ultrasound evaluation of ovarian activity under oral contraceptives. Contraception 47:583–590.

Iguchi MY, Handelsman L, Bickel WK, Griffiths RR. 1993. Benzodiazepine and sedative use/abuse by methadone maintenance clients. Drug Alcohol Depend 32:257–266.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12.

Kasper S, Anghelescu I, Dienel A. 2010a. Efficacy of Silexan (WS® 1265) in Patients with Restlessness and Sleep Disturbance. Annual Congress of the German Society for Psychiatry and Psychotherapy (DGPPN). Berlin, Germany.

Kasper S, Dienel A. 2011. Effects of Silexan® on human cytochrome P450 activity and contraceptive efficacy of a combined oral contraceptive. Annual Congress of the German Society for Psychiatry and Psychotherapy (DGPPN). Berlin, Germany.

Kasper S, Gastpar M, Muller WE, Volz HP, Moller HJ, Dienel A, Schlafke S. 2010b. Efficacy and safety of silexan, a new, orally administered lavender oil preparation, in subthreshold anxiety disorder – evidence from clinical trials. Wien Med Wochenschr 160:547–556.

Kasper S, Gastpar M, Müller WE, Volz HP, Möller HJ, Dienel A, Schläfke S. 2010c. 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.

Kasper S, Gastpar M, Müller WE, Volz HP, Möller HJ, Schläfke S, Dienel A. 2011. No withdrawal symptoms after discontinuation of Silexan®. Annual Congress of the German Society for Psychiatry and Psychotherapy (DGPPN). Berlin, Germany.

Kendall PC, Finch AJ Jr, Auerbach SM, Hooke JF, Mikulka PJ. 1976. The State-Trait Anxiety Inventory: a systematic evaluation. J Consult Clin Psychol 44:406–412.

Kessler RC, Brandenburg N, Lane M, Roy-Byrne P, Stang PD, Stein DJ, Wittchen HU. 2005. Rethinking the duration requirement for generalized anxiety disorder: evidence from the National Comorbidity Survey Replication. Psychol Med 35: 1073–1082.

Lader MH. 1999. Limitations on the use of benzodiazepines in anxiety and insomnia: are they justified? Eur Neuropsychopharmacol 9:S399–S405.

Lewinsohn PM, Shankman SA, Gau JM, Klein DN. 2004. The prevalence and co-morbidity of subthreshold psychiatric conditions. Psychol Med 34:613–622.

Longo LP, Johnson B. 2000. Addiction: Part I. Benzodiazepines–side effects, abuse risk and alternatives. Am Fam Physician 61: 2121–2128.

National Institute of Mental Health. 1970. 12 - CGI. Clinical Global Impressions. In: Guy W, editor. EDCEU Assessment in Psychopharmacology. Rockville, MD: U.S. National Institute of Mental Health, Psychopharmacology Research Branch, pp. 217–222.

Onyett SR. 1989. The benzodiazepine withdrawal syndrome and its management. J R Coll Gen Pract 39:160–163.

Perry R, Terry R, Watson LK, Ernst E. 2012. Is lavender an anxiolytic drug? A systematic review of randomised clinical trials. Phytomedicine 19:825–835.

Petursson H. 1994. The benzodiazepine withdrawal syndrome. Addiction 89:1455–1459.

Pincus HA, Davis WW, McQueen LE. 1999. 'Subthreshold' mental disorders. A review and synthesis of studies on minor depression and other 'brand names'. Br J Psychiatry 174:288–296.

Rickels K, Garcia-Espana F, Mandos LA, Case GW. 2008. Physician Withdrawal Checklist (PWC-20). J Clin Psychopharmacol 28:447–451.

Setzer WN. 2009. Essential oils and anxiolytic aromatherapy. Nat Prod Commun 4:1305–1316.

Uehleke B, Schaper S, Dienel A, Schläfke S, Stange R. 2012. Phase II trial on the effects of Silexan in patients with neurasthenia, post-traumatic stress disorder or somatization disorder. Phytomedicine 19:665–671.

Volz HP, Gastpar M, Kasper S, Möller HJ, Müller WE. 2011. Subsyndromale Angststörungen: Definition, Messparameter, Epidemiologie. J Neurol Neurochir Psychiatr 12:162–167.

Ware JE Jr, Sherbourne CD. 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473–483.

Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, et al. 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 21:655–679.

Wittchen HU, Kessler RC, Beesdo K, Krause P, Hofler M, Hoyer J. 2002. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry 63:24–34.

Woelk H, Schläfke S. 2010. 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.

Zung WW. 1971. A rating instrument for anxiety disorders. Psychosomatics 12:371–379.