Silexan, an orally administered Lavandula oil preparation, is effective in the treatment of 'subsyndromal' anxiety disorder: a randomized, double-blind, placebo controlled trial

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This study was performed to investigate the anxiolytic efficacy of silexan, a new oral lavender oil capsule preparation, in comparison to placebo in primary care. In 27 general and psychiatric practices 221 adults suffering from anxiety disorder not otherwise specified (*Diagnostic and Statistical Manual of Mental disorders*–IV 300.00 or *International Statistical Classification of Diseases and Related Health Problems, Tenth revision F41.9*) were randomized to 80 mg/day of a defined, orally administered preparation from Lavandula species or placebo for 10 weeks with visits every 2 weeks. A Hamilton Anxiety Scale (HAMA) total score ≥ 18 and a total score >5 for the Pittsburgh Sleep Quality Index (PSQI) were required. The primary outcome measures were HAMA and PSQI total score decrease between baseline and week 10. Secondary efficacy measures included the Clinical Global Impressions scale, the Zung Self-rating Anxiety Scale, and the SF–36 Health Survey Questionnaire. Patients treated with silexan showed a total score decrease by 16.0 ± 8.3 points (mean ± SD, 59.3%) for the HAMA and by 5.5 ± 4.4 points (44.7%) for the PSQI compared to 9.5 ± 9.1 (35.4%) and 3.8 ± 4.1 points (30.9%) in the placebo group ($P<0.01$ one-sided, intention to treat). Silexan was superior to placebo regarding the percentage of responders (76.9 vs. 49.1%, $P<0.001$) and remitters (60.6 vs. 42.6%, $P=0.009$). Lavandula oil preparation had a significant beneficial influence on quality and duration of sleep and improved general mental and physical health without causing any unwanted sedative or other drug specific effects. Lavandula oil preparation silexan is both efficacious and safe for the relief of anxiety disorder not otherwise specified. It has a clinically meaningful anxiolytic effect and alleviates anxiety related disturbed sleep. *Int Clin Psychopharmacol* 25:277–287

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Background

Lavender is an aromatic branched perennial evergreen shrub that has been used traditionally as a cosmetic herb, and owes its common name to the Latin lavare, to wash. In European, Arabic and Asian folk medicine, lavender, predominantly as an oil for inhalation or topical application, has been used for a variety of indications (British Herbal Medicine Association, 1996; Chu and Kemper, 2001). The German Commission E, an independent body appointed by the German Federal Health Agency in 1978 to analyze and assess the information regarding herbal medicines compiled from evidence based as well as from traditional sources, has approved lavender flowers (*Lavandulae flos*) for the treatment of restlessness, insomnia, and nervous disorders of the intestines (Bundesgesundheitsamt, 1984).

Psychological and psychiatric research involving lavender preparations has been focused on the drugs' relaxing, anxiolytic and mood alleviating effects [e.g. (Motomura *et al.*, 2001; Louis and Kowalski, 2002; Morris, 2002; Akhondzadeh *et al.*, 2003; Field *et al.*, 2005; Lehrner *et al.*, 2005; Lin *et al.*, 2007; Bradley *et al.*, 2009; McCaffrey *et al.*, 2009)]. Anxiety disorders are among the most common types of mental illnesses (Hidalgo and Davidson, 2001), with a 12-month prevalence of approximately 17% and a lifetime prevalence of almost 25% in the USA (Kessler *et al.*, 1994). The core symptoms of anxiety are feelings of apprehension, uncertainty and fear. They are often accompanied by a variety of other psychological and somatic manifestations such as restlessness, nervous disorders of the intestines, and disturbance of sleep with impairment of sleep initiation, duration, or quality (Ohayon *et al.*, 2000). Despite its high prevalence, anxiety disorder is a seriously undertreated condition, and a recent mental health survey suggests that more than half of affected patients do not receive appropriate treatment (Andrews and Carter, 2001). One of the reasons for this

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observation may be that patients are reluctant to take, or physicians are reluctant to prescribe, drugs like tranquilizers, antidepressants and neuroleptics that may cause disturbing side effects or have an addictive potential (Lader, 1999). Lavender could be a gentle and thus more acceptable treatment option, as the drug has been found to be virtually devoid of side effects (Bundesgesundheitsamt, 1984), except for very rare cases of allergic reactions (Coulson and Khan, 1999) and for gastrointestinal complaints after excessive intake (Leung and Foster, 1996).

Lavender oil contains more than 160 substances, the main constituents of which are linalool, linalyl acetate, 1.8-cineole, β-ocimene, terpinen-4-ol and camphor, whose therapeutic effect in man has been investigated and reviewed only as a whole (Cavanagh and Wilkinson, 2002). In rats linalool has been shown to inhibit the glutamate binding in the cerebral cortex. This effect has been suggested to contribute to the effect of lavender oil on the central nervous system (Elizabetsky *et al.*, 1995).

The anxiolytic action of lavender is supported by several small or medium-sized clinical trials (Buckle, 1993; Dunn *et al.*, 1995; Hardy *et al.*, 1995; Hudson, 1996; Wolfe and Herzberg, 1996; Itai *et al.*, 2000; Louis and Kowalski, 2002; Lehrner *et al.*, 2005). In a reference controlled study, Itai *et al.* (Itai *et al.*, 2000) investigated the effects of lavender oil aromatherapy on mood and anxiety in 14 women undergoing chronic hemodialysis. Patients treated with lavender oil showed significant decreases in anxiety measured with the Hamilton Anxiety Scale (HAMA) (Hamilton, 1976). In a trial reported by Dunn *et al.* (1995), 122 critically ill patients in a hospital intensive care unit received aromatherapy massage with lavender oil, massage without aromatherapy, or a period of rest. Individuals exposed to lavender aromatherapy reported significant improvements in their perceived anxiety levels compared with those in the control groups. Buckle (1993) compared aromatherapy massage with two different species of lavender (*Lavandula angustifolia* and *Lavandula hybridi*) in a double-blind trial whose participants were 28 patients recovering from bypass surgery. Both the species were determined to decrease the participants' anxiety levels. The findings from these trials are supported by the results of several other investigations in which lavender aromatherapy as well as oral administration of lavender preparations had an antidepressant, psychologically relaxing, and general mood alleviating effect [see (Chu and Kemper, 2001) for an overview]. Furthermore, lavender was also shown to have a beneficial effect on sleep (Hardy *et al.*, 1995; Hudson, 1996; Wolfe and Herzberg, 1996).

Unfortunately, some of the trials investigating the anxiolytic efficacy of lavender preparations were methodologically not convincing (e.g. small sample size, inadequate control). Furthermore, all trials published to date were performed in highly specific patient populations (e.g. patients with a terminal illness or on intensive care), and in patients in whom anxiety was triggered by a well-defined situational context (imminent medical intervention expected to be painful or dangerous; terminal disease).

We report on a randomized, double-blind, placebo controlled trial in which the efficacy and tolerability of an orally administered, quality-selected, well-defined preparation from Lavandula angustifolia in an immediate release capsule, silexan [Silexan is the active substance of LASEA (W. Spitzner Arzneimittelfabrik GmbH, Ettlingen)], were investigated in a population of patients with 'subsyndromal' anxiety disorder (Lawrence and Brown, 2009) that is typical in a primary care setting and is commonly labelled anxiety disorder not otherwise specified (NOS). The investigated Lavandula oil preparation silexan is currently the only pharmaceutical quality lavender oil that is intended for oral administration.

Methods

Protocol, design, and objectives

We performed a randomized, double-blind, multi-centre trial according to an adaptive two-stage design, to prove the anxiolytic efficacy of Lavandula oil preparation by demonstrating superiority over placebo. Following a single-blind placebo screening and washout phase of 3–7 days' duration participants meeting the selection criteria were randomized to 10 weeks of double-blind treatment with Lavandula oil preparation or placebo during which efficacy and safety assessments were performed every 2 weeks. The study protocol was reviewed and approved by an independent ethics committee. All patients provided written informed consent. The principles of Good Clinical Practice and the Declaration of Helsinki were adhered to.

Participants

In 27 general and psychiatric primary care centres in Germany male and female out-patients between 18 and 65 years of age were recruited who suffered from an anxiety disorder according to *Diagnostic and Statistical Manual of Mental Disorders*-IV (American Psychiatric Association, 2000) 300.00 or International statistical classification of diseases and related health problems, tenth revision (World Health Organization, 1992) F41.9. These diagnostic categories include disorders with prominent anxiety or phobic avoidance that do not meet criteria for any other specific anxiety disorder, adjustment disorder with anxiety, or adjustment disorder with mixed anxiety and depressed mood (e.g. mixed disorder with anxiety and depression, social phobia with anxiety related to medical conditions such as Parkinson's disease, dermatological conditions or anorexia nervosa, or situations in which the clinician has concluded that anxiety disorder is present but he/she is unable to determine whether it is primary, because of a general medical condition, or substance induced). The diagnosis was established by each centre's investigator personally based

on the International statistical classification of diseases and related health problems, tenth revision Diagnostic and Management Guidelines for Mental Disorders in Primary Care (World Health Organization, 1996). It applies to patients with symptoms of anxiety disorder, or adjustment disorder with anxiety disorder, or mixed anxiety and depressed mood. The category generally includes disorders with prominent anxiety or phobic avoidance that do not meet criteria for any specific anxiety disorder, adjustment disorder with anxiety, or adjustment disorder with mixed anxiety and depressed mood. A HAMA total score ≥ 18 points and ≥ 2 points for items 'Anxious mood' and 'Insomnia', as well as a total score > 5 points for the Pittsburgh Sleep Quality Index (PSQI) (Buysse *et al.*, 1989) were required at the beginning and end of the screening phase. Female patients of childbearing potential had to have a negative pregnancy test and had to use adequate contraception. There were no restrictions regarding ethnic groups.

Anyone with a HAMA total score decrease $\geq 25\%$ during run-in, or with any clinically important psychiatric or neurological diagnosis other than anxiety disorder according to the criteria above, risk of suicide, or substance abuse disorder was excluded. Other psychotropic medication or muscle relaxants as well as psychotherapy were not allowed during study participation (in case of earlier medication an appropriate wash-out period had to be observed).

Interventions, blinding

We investigated a defined preparation from Lavandula species. Soft gelatine capsules containing 80 mg of silexan or identically matched placebo capsules were used. 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 Lavandula oil preparation capsules, that is, 0.08 mg of lavender oil per capsule of placebo. The study participants were instructed to swallow the capsules unchewed.

During the 3–7 days single-blind screening period all patients received one capsule of placebo once daily in the morning. Following randomization eligible patients took one capsule of Lavandula oil preparation or placebo per day for a scheduled period of 10 weeks.

Measures of efficacy and safety

The primary outcome measures were changes of the total scores of the HAMA (Hamilton, 1976) (observer rating of anxiety level) and of the PSQI (Buysse *et al.*, 1989) (self rating of sleep quality) between baseline (i.e. start of randomized treatment) and the final examination at week 10. Both rating scales were completed at screening and baseline as well as bi-weekly during randomized treatment (HAMA) or at weeks 2 and 6 (PSQI). Patients with a HAMA total score decrease $\geq 50\%$ of the baseline value during randomized treatment, or with a PSQI total score decrease $\geq 50\%$, were assessed to be responders. Those who showed a HAMA total score of less than 10 points or a PSQI total score of less than 6 points at treatment end were classified as being in remission. Secondary outcome measures of treatment efficacy also included the Clinical Global Impressions (CGI) (National Institute of Mental Health, 1970) observer rating scale, the Zung Self-rating Anxiety Scale (SAS) (Zung, 1971), and the SF-36 Health Survey Questionnaire (Ware and Sherbourne, 1992). The assessments of safety and tolerability were based on spontaneous reports of adverse events (AEs), physical and ECG examinations as well as vital signs and routine laboratory measurements.

Random sequence generation, allocation concealment, implementation

The random code was generated using a validated computer program. Patients still meeting the selection criteria at baseline were randomized at a ratio of 1 : 1 to Lavandula oil preparation or placebo. Randomization was performed in blocks stratified by trial centre; however, the investigators were not informed about the random block size until completion of the trial in order to ensure the blinding of the interventions. Upon inclusion into randomized treatment the local investigator allocated each patient the lowest available number. The study drugs were dispensed to the centres in numbered containers.

Statistical methods, sample size

Confirmatory analysis of the primary outcome measures was performed using a two-stage design. In this design two parts of a trial are separated by a pre-planned, adaptive interim analysis that offers options for early stopping or sample size re-calculation based on unblinded data. If the study is continued with a second part after the interim analysis (which was indeed the case in this trial) the P values obtained in both parts are combined using the Fisher's combination test. It has been shown that this procedure assures strong control of the global type I error probability (Bauer and Köhne, 1994).

The global type I error rate was $\alpha = 0.025$ (one-sided). At the interim look null hypotheses could be rejected if a local boundary of $\alpha_1 = 0.0038$ was not exceeded. Accepting a null hypothesis for futility during the interim analysis was not an option (nonstochastic curtailment): in case of an interim analysis P value $> \alpha_1$ the associated null hypothesis was to be tested again in the final analysis after the second part of the trial in which the P values determined separately for both parts are combined using the Fisher's combination test. With this study's local boundaries for the interim analysis this implies that the null hypothesis can be rejected when the product of the P values from both parts of the trial falls below $c_\alpha = 0.0038$ (Bauer and Köhne, 1994). Multiple testing of two primary endpoints was accounted for by a closed

testing procedure according to which superiority of Lavandula oil preparation over placebo was to be tested separately for the HAMA and the PSQI (using independent samples *t*-tests) after rejection of a global null hypothesis predicting no superiority of Lavandula oil preparation in any of the primary outcome measures [based on the O'Brien's Ordinary Least Squares (OLS) test (O'Brien, 1984)]. Application of the decision strategy for the closed test procedure in studies with an adaptive interim analysis (Kieser *et al.*, 1999) assures control of the experiment-wise type I error rate $\alpha = 0.025$ (one-sided).

Missing values were replaced by carrying the last observation forward (LOCF). The primary analysis was based on the intention-to-treat analysis set (ITT) that included all patients who received at least one dose of study medication and who had at least one post baseline outcome assessment for both primary outcome measures. An additional per protocol (PP) analysis was performed as a sensitivity analysis. HAMA and PSQI total score change between baseline and week 10 effect sizes were determined as the difference between the treatment groups' mean values divided by their pooled standard deviation (Cohen, 1988) (an effect size > 0 denotes an advantage of Lavandula oil preparation over placebo). All secondary efficacy and safety measures were analyzed descriptively. The sample size calculation was based on both, HAMA total score change and PSQI total score change. Assuming a difference between the treatment groups' mean values of 2.5 points and a common standard deviation of 6.0 points for the HAMA total score change as well as a difference between the treatment groups' mean values of 1.0 point and a common standard deviation of 2.7 points for the PSQI total score change 2×110 patients were required to achieve a power of 80% for testing the single null-hypotheses each with a one-sided *t*-test using the Bonferroni adjusted type I error rates of $\alpha/2 = 0.0125$. It was expected that the application of the OLS closed testing procedure would lead to an increase in power.

Results

Recruitment, participant flow

Between September 2004 and April 2005, 233 Caucasian patients were included and 221 were randomized and treated in 27 centres in Germany. Five case report forms from one centre were excluded from all analyses because of concerns regarding the authenticity of the data, and thus 216 patients (Lavandula oil preparation: 107; placebo: 109) were analyzed. Reasons for non-randomization, premature termination or exclusion from the ITT or from the PP analysis are shown in Fig. 1. For Lavandula oil preparation and placebo, respectively, 104 and 108 patients were considered in the ITT analysis of treatment efficacy (first part of study: Lavandula oil preparation 78, placebo 84; second part: Lavandula oil preparation 26, placebo 24). All decisions regarding patient eligibility were obtained before code breaking. The numbers of patients terminating their trial participation before the scheduled end as well as the number of study participants with relevant protocol violations (i.e. those which might cause bias regarding the primary outcome measures) were comparable in both study groups.

Baseline data

Baseline demographic and clinical measures were comparable in both treatment groups (Table 1). About ¾ of the study participants were female. In each group more than 50% of the patients had HAMA total score ≥ 26 and and/or a PSQI total score ≥ 12 points at baseline. For CGI item 1 (severity of illness) there was a tendency towards a slightly larger percentage of patients with more severe impairment in the placebo group whereas all other psychiatric self and observer rating scales showed only negligible baseline treatment group differences.

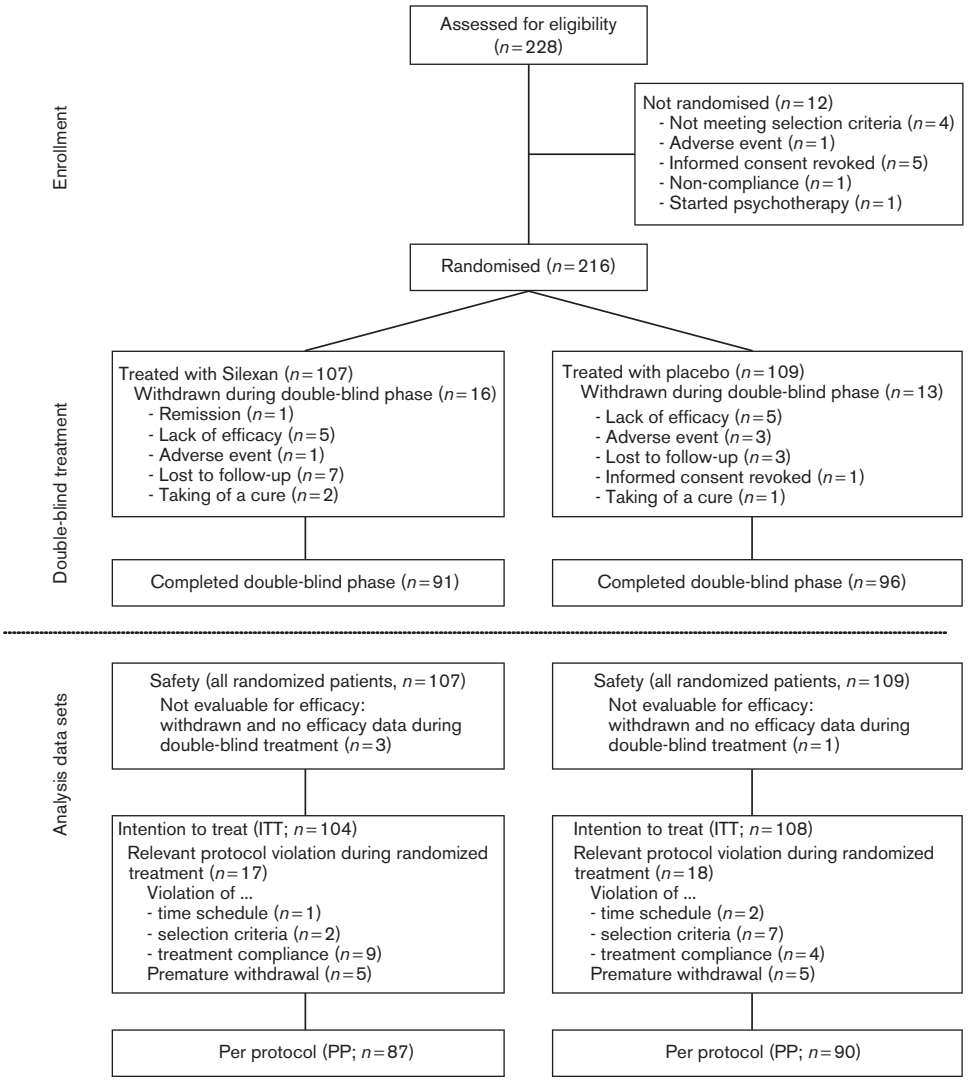
Investigational treatment

In the ITT data set average study drug intake (assessed by medication counting) was 100.3 ± 5.0% (mean ± SD) of the prescribed amount for Lavandula oil preparation and 100.3 ± 4.1% for placebo, with interquartile ranges of 100.0–101.5% and 98.6–101.5% for Lavandula oil preparation and placebo, respectively. Nine patients in the Lavandula oil preparation group and four patients treated with placebo had to be excluded from the PP analysis for insufficient treatment compliance (Fig. 1).

Efficacy

The change statistics for the total scores of the HAMA and the PSQI (primary outcome measures) are summarized in Table 2. With a local type I error level of $\alpha_1 = 0.0038$ (one-sided) the global null hypothesis of the OLS test was rejected in the interim analysis (ITT: $P < 0.001$), and thus confirmatory treatment group comparisons for the two main outcomes were performed. With respect to HAMA total score reduction superiority of Lavandula oil preparation over placebo was already shown after the first part of the trial ($P < 0.001$; confirmatory ITT analysis). For the PSQI a *P* value of $P_1 = 0.007 > \alpha_1$ was determined in the interim analysis. Accordingly, the hypothesis was tested again after the second part of the trial ($P_2 = 0.047$). In the combination test the critical rejection boundary was not exceeded ($0.007 \times 0.047 = 0.00033 < c_\alpha = 0.0038$) and superiority of Lavandula oil preparation over placebo in improving sleep quality as determined with the PSQI was proven to be significant. Table 2 also shows that the results of the ITT analysis were fully supported by the PP evaluation which led to the same conclusions. Furthermore, the treatment effects observed during the first and second part of the trial were comparable, and differences in *P* values or confidence interval width were mainly attributable to loss of power caused by the lower sample size

Fig. 1



Patient accountability and analysis data sets.

in the second part. For HAMA and PSQI total score change between baseline and week 10 effect sizes of 0.75 and 0.40 were determined, respectively (ITT, LOCF).

Table 3 shows the main results for the psychiatric scales included as secondary efficacy measures. For anxiety the data obtained in the SAS fully confirmed the results of the HAMA. Compared to the placebo group patients treated with Lavandula oil preparation showed greater improvements of mental and physical health (SF-36), and larger percentages of patients treated with the herbal essence were only borderline or not at all ill, and showed moderate or marked improvements at treatment end (CGI).

Figure 2 shows the HAMA total score time course for the pooled data of both parts of the trial (ITT). Between baseline and week 10 the total score in the Lavandula oil preparation group decreased from 26.8 ± 5.4 points at baseline to 10.9 ± 8.7 points at treatment end (corresponding to an average decrease by 59.3% of the baseline value) and from 27.1 ± 5.3 points to 17.5 ± 10.4 points (35.4% decrease) in the placebo group. Although the average HAMA total score of patients treated with Lavandula oil preparation continued to decrease until the end of the period of observation the patients exposed to placebo showed no further improvements beyond week 8. For the total score of the PSQI (Figure 3) decreases from 12.3 ± 2.9 to 6.8 ± 4.2 points (44.7% decrease) and from 12.6 ± 3.0 to 8.7 ± 4.5 points (30.9% decrease) were observed for Lavandula oil preparation and placebo, respectively.

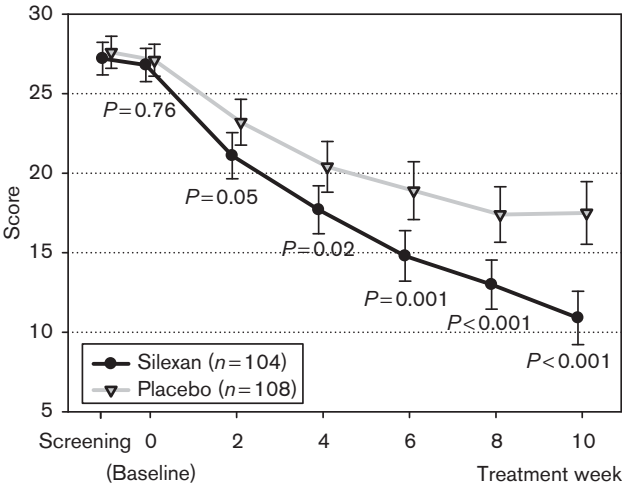
As shown in Fig. 4 on the basis of the total scores of the HAMA and the PSQI 76.9% of the patients treated with

Table 1 Baseline characteristics

	Silexan ($n=104$)	Placebo ($n=108$)	P value
Sex			
Female	76 (73.1%)	83 (76.9%)	0.526[a]
Male	28 (26.9%)	25 (23.2%)	
Age (years)	45.6 ± 11.4	46.6 ± 11.3	0.549[a]
HAMA total score	26.8 ± 5.4	27.1 ± 5.3	0.755[b]
PSQI total score	12.3 ± 2.9	12.6 ± 3.0	0.514[b]
SAS total score	60.1 ± 9.9	61.1 ± 10.1	0.447[b]
SF-36 physical health	51.7 ± 21.7	53.2 ± 22.1	0.632[b]
SF-36 mental health	32.3 ± 17.4	32.6 ± 21.2	0.899[b]
CGI item 1 –Severity of illness			
Mildly ill	8 (7.7%)	1 (0.9%)	0.051[c]
Moderately ill	34 (32.7%)	34 (31.5%)	
Markedly ill	58 (55.8%)	66 (61.1%)	
Severely ill	4 (3.9%)	7 (6.5%)	

Intention-to-treat; sample characteristics and two-sided P values for treatment group comparison; absolute frequency (%), or mean ± SD.
For the HAMA, PSQI, and the SAS, higher scores indicate more severe impairment whereas lower scores indicate more severe impairment for the SF-36.
CGI, clinical global impressions; HAMA, Hamilton anxiety scale; PSQI, Pittsburgh sleep quality index; SAS, Zung self-rating anxiety scale; SF-36, SF-36 health survey questionnaire.
[a]χ^2-test.
[b]t-test.
[c]Mantel-Haenszel χ^2-test.

Fig. 2



Hamilton Anxiety Scale total score time course (means, 95% confidence intervals and two-sided t-test P values; pooled data, intention-to-treat, last observation carried forward).

Table 2 Hamilton anxiety scale and Pittsburgh sleep quality index total score decrease, baseline – week 10

Scale	Analysis	Study part	Silexan	Placebo	Confidence interval	P value
Hamilton anxiety scale	ITT	1st part	16.4 ± 7.9 ($n=78$)	10.8 ± 8.8 ($n=84$)	3.0–8.2	<0.001
		2nd part	14.7 ± 9.2 ($n=26$)	5.0 ± 8.7 ($n=24$)	4.6–14.8	<0.001
		Pooled data	16.0 ± 8.3 ($n=104$)	9.5 ± 9.1 ($n=108$)	4.1–8.8	<0.001
	PP	1st part	16.9 ± 7.9 ($n=66$)	11.5 ± 8.9 ($n=72$)	2.6–8.3	0.001
		2nd part	14.0 ± 9.2 ($n=21$)	5.9 ± 9.0 ($n=18$)	2.1–13.9	0.005
		Pooled data	16.2 ± 8.2 ($n=87$)	10.4 ± 9.1 ($n=90$)	3.3–8.4	<0.001
Pittsburgh sleep quality index	ITT	1st part	5.8 ± 3.9 ($n=78$)	4.3 ± 4.0 ($n=84$)	0.3–2.8	0.007
		2nd part	4.7 ± 5.5 ($n=26$)	2.3 ± 4.2 ($n=24$)	−0.4 to 5.2	0.047
		Pooled data	5.5 ± 4.4 ($n=104$)	3.8 ± 4.1 ($n=108$)	0.6–2.9	0.002
	PP	1st part	5.9 ± 4.0 ($n=66$)	4.4 ± 4.2 ($n=72$)	0.2–2.9	0.007
		2nd part	4.5 ± 5.2 ($n=21$)	2.6 ± 4.2 ($n=18$)	−1.2 to 5.1	0.105
		Pooled data	5.6 ± 4.3 ($n=87$)	4.0 ± 4.2 ($n=90$)	0.3–2.8	0.008

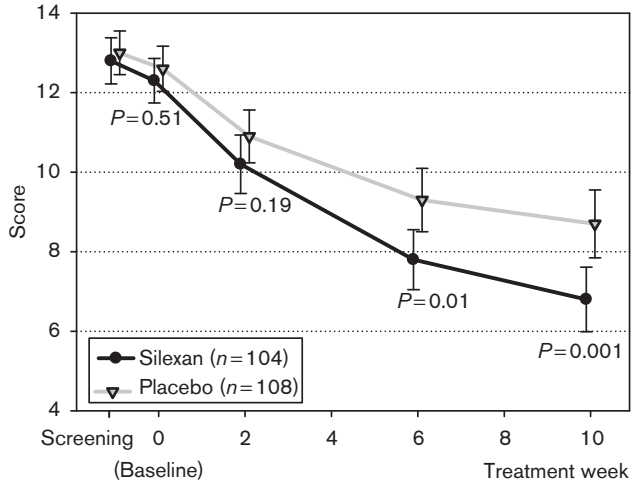
Mean ± SD, 95% confidence interval and one-sided t-test p-value for difference between means; last observation carried forward.
ITT, intention-to-treat; PP, per protocol.

Table 3 Secondary efficacy measures

	Silexan ($n=104$)	Placebo ($n=108$)	P value
SAS	−15.6 ± 11.4	−11.1 ± 12.2	0.003[a]
Total score change, week 10 – baseline			
SF-36	($n=97$)	($n=102$)	
Subscore change, week 10 – baseline			
Physical health	20.5 ± 22.6	10.8 ± 19.8	<0.001[a]
Mental health	32.5 ± 24.1	19.8 ± 22.4	<0.001[a]
CGI item 1 – Severity of illness	51 (49.0%)	21 (19.4%)	<0.001[b]
Patients not at all or borderline mentally ill, week 10			
CGI item 2 – Global improvement	77 (74.0%)	44 (40.7%)	<0.001[b]
Patients markedly or moderately improved, week 10			
CGI item 3 – Efficacy index	3.2 ± 1.0 ($n=96$)	2.3 ± 1.2 ($n=103$)	<0.001[a]
Patients markedly or moderately improved, week 10			

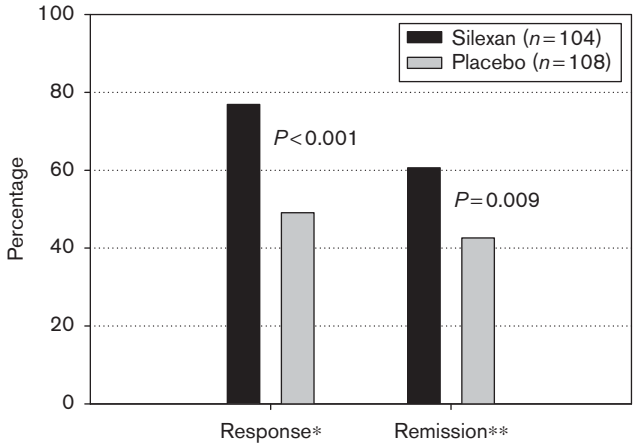
Intention-to-treat; sample characteristics and P values for treatment group comparison; absolute frequency (%), or mean ± SD.
CGI, clinical global impressions; SAS, Zung self-rating anxiety scale; SF-36, SF-36 health survey questionnaire.
For the SF-36 and CGI item 3 higher values indicate more favourable results whereas lower values indicate more favourable results for the SAS.
[a]t-test, one-sided.
[b]Mantel-Haenszel χ^2-test, two-sided, for original (uncategorized) distribution.

Fig. 3



Pittsburgh Sleep Quality Index total score time course (means, 95% confidence intervals and two-sided *t*-test *P* values; pooled data, intention-to-treat, last observation carried forward).

Fig. 4



Responders and Remitters based on Hamilton Anxiety Scale (HAMA) and Pittsburgh Sleep Quality Index (PSQI); relative frequency and two sided *P* value of the χ^2-test for comparing the treatment groups; pooled data, intention-to-treat, last observation carried forward). * HAMA or PSQI total score decrease of at least 50% compared to baseline; **HAMA total score <10 or PSQI total score <6 at treatment end.

Lavandula oil preparation and 49.1% of those in the placebo group were responders ($P < 0.001$), and 60.6% compared to 42.6% were in remission when completing treatment ($P = 0.009$). In an analysis of individual items Lavandula oil preparation was superior to placebo at a one-sided P value ≤ 0.025 for 13 of the 14 items of the HAMA, and efficacy was thus demonstrated for the Psychic Anxiety as well as for the Somatic Anxiety subscales of the instrument (both $P < 0.001$ one-sided; ITT, pooled data). Among the seven components of the PSQI Lavandula oil preparation was particularly effective in improving the subjective quality of sleep ($P = 0.003$), sleep latency ($P = 0.034$), daytime tiredness ($P = 0.014$), and subjectively perceived sleep duration ($P = 0.001$).

Table 4 No. (%) of patients with adverse events that occurred in at least 3 patients in 1 group during randomized treatment

	Silexan ($n=107$) (%)	Placebo ($n=109$) (%)
Influenza	6 (5.6)	3 (2.8)
Dyspepsia	5 (4.7)	2 (1.8)
Headache	3 (2.8)	4 (3.7)
Dizziness	2 (1.9)	4 (3.7)
Gastroenteritis	0 (0.0)	5 (4.6)
Eructation	4 (3.7)	0 (0.0)
Nausea	0 (0.0)	3 (2.8)
Bronchitis	1 (0.9)	4 (3.7)
Arthralgia	0 (0.0)	3 (2.8)
Any adverse events[a]	39 (36.4)	35 (32.1)

Safety analysis set.
[a]Includes events observed in fewer than three patients in one group that are not shown in the table.

Safety/tolerability

During randomized treatment 39 (36.4%) of 107 patients exposed to Lavandula oil preparation reported 55 AE and 35 (32.1%) of 109 patients exposed to placebo reported 68 AE (safety analysis set). This corresponded to one AE in 126 days of exposure to Lavandula oil preparation and to one event in 107 days of placebo treatment. According to MedDRA System Organ Classes the most frequently reported AEs were related to infections and infestations, affecting 12.1% (13 of 107) of the patients in the Lavandula oil preparation group and 17.4% (19 of 109) of the patients in the placebo group, followed by gastrointestinal disorders (Lavandula oil preparation 13.1%, placebo 9.2%) and nervous system disorders (8.4 and 9.2%, respectively). AEs occurring in at least three patients in one treatment group are shown in Table 4.

In 12 patients in the Lavandula oil preparation group (11.2%) and in 14 patients in the placebo group (12.8%) a causal relationship between an AE and the investigational treatment could not be excluded (blind assessment). Among the potentially attributable AEs the most frequent in both treatment groups were gastrointestinal disorders. Two serious AEs were reported in each treatment group. Both events observed under Lavandula oil preparation (asthma attack, abdominal pain because of gynaecological disorder) were not attributable. All AEs necessitating premature withdrawal from the trial (Fig. 1) were also not related.

Discussion

To date the most commonly used drugs in the pharmacological treatment of anxiety are serotonin reuptake inhibitors (SRIs) and benzodiazepines (Bandelow *et al.*, 2008).

The latter's well-known side effects include drowsiness, fatigue, confusion and disorientation (notably in the elderly), dizziness, decreased concentration, impaired memory, dry mouth, and blurred vision. They can impair the ability to drive or operate machinery and may thus seriously interfere with essential activities of professional and private life. They lower the tolerance to alcohol and have been reported to cause physical and psychological dependence and withdrawal symptoms (Longo and Johnson, 2000). SRIs, on the other hand, may cause sedation and fatigue, gastrointestinal disturbances, agitation or insomnia (Preskorn, 1995; Trindade *et al.*, 1998). The risks and inconveniences associated with available anxiolytic medication may thus contribute to the observation that anxiety disorder is a seriously undertreated condition (Andrews and Carter, 2001).

This study presents the results of the first double-blind, randomized, placebo-controlled trial that investigated the anxiolytic efficacy of orally administered lavender essence. The study shows that silexan at a dose of 80 mg/day has a clinically meaningful and statistically significant anxiolytic effect with an advantage of at least four points in HAMA total score reduction after 10 weeks on the population level (lower bound of confidence interval for difference in means, ITT, pooled data; see Table 2). The anxiolytic effect of the herbal essence was clinically detectable after 2 weeks of randomized treatment and was statistically significant at week 4 and all later visits. An extrapolation of the HAMA total score time course in Fig. 2 suggests that additional advantages for silexan may be expected when continuing treatment beyond week 10.

Surprisingly, there appear to be no other published therapeutic trials in patients suffering from 'subsyndromal' anxiety disorder NOS although this is quite a common condition particularly in primary care. The validity of a direct comparison of our results with the literature is limited by the fact that most studies in anxiety have been performed in patients with generalized anxiety disorder (GAD). Individuals with anxiety disorder NOS present with clinically significant symptoms, but they tend to reported less worry, negative affect, depression, and comorbidity than those with GAD (Lawrence and Brown, 2009). However, although our results cannot be generalised to GAD and other defined anxiety disorders and vice versa, a comparison may nevertheless be interesting in the absence of more suitable data.

With an average of 16 points at week 10 of randomized treatment the HAMA total score reduction for silexan in anxiety disorder NOS was comparable to the effect of bromazepam, oxazepam and Kava observed in other research [e.g. (Woelk *et al.*, 1999)] and more pronounced than in case of escitalopram and paroxetine [reductions of 15.3 and 13.3 points, respectively, after 24 weeks (Bielski *et al.*, 2005) or duloxetine (11.1 point reduction after 10 weeks) (Allgulander *et al.*, 2007) in patients suffering from GAD. In their recent meta-analysis of 21 double-blind, placebo-controlled trials in patients with GAD Hidalgo *et al.* (Hidalgo *et al.*, 2007) have determined average effect sizes for HAMA total score change versus baseline of 0.50 for pregabalin, 0.45 for hydroxyzine, 0.42 for venlafaxine XR, 0.38 for benzodiazepines, 0.35 for selective serotonin reuptake inhibitors (SSRIs) and 0.17 for buspirone, compared with an effect size of 0.75 for silexan computed in this trial in anxiety disorder NOS. It is important to note that the significant reduction of anxiety related symptoms in patients treated with silexan was not only evident in the judgment of the investigators but was also perceived by the study participants subjectively according to the results of the SAS self-rating questionnaire.

These findings are consistent with the results of in-vitro studies which suggest that lavender oil may have anxiolytic and antidepressant properties and which thus shed light on the drug's potential mode of action: Lavender oil potentiated the binding of GABA on $GABA_A$ receptors in Xenopus oocytes (Aoshima and Hamamoto, 1999) and showed spasmolytic activity in a guinea-pig ileum smooth muscle preparation (Lis-Balchin and Hart, 1999). Furthermore, linalyl acetate and linalool drastically reduced the electrically-evoked concentrations of rat phrenic-hemidiaphragm in a dose-dependant manner (Ghelardini *et al.*, 1999), and linalool inhibited glutamate binding in rat cerebral cortex (Elizabetsky *et al.*, 1995) as well as acetylcholine release and altered ion channel function at the neuromuscular junction (Re *et al.*, 2000).

Disturbed sleep has been observed to be among the most frequent accompanying disorders of generalized anxiety (Ohayon *et al.*, 2000). To verify the beneficial effect of lavender on sleep derived from previous research (Hardy *et al.*, 1995; Hudson, 1996; Wolfe and Herzberg, 1996) we decided to perform our study in a patient population whose pathology included clinically relevant sleep disturbances. Indeed, silexan had a significant beneficial influence on the patients' duration and quality of sleep and reduced their daytime tiredness which can be regarded as an important contribution to their over-all quality of life. The effect was already notable after 2 weeks of treatment and became statistically significant from week 6 on.

The herbal essence also significantly improved the perception of general mental and physical health without causing any unwanted sedative effects. This combination of an alleviation of anxiety-related symptoms and improved general and physical health was also reflected in the investigators' global impression of the patients' state according to the CGI. The advantages of silexan over placebo were thus completely stable across the two parts of the trial, between the ITT and PP analyses as well as in all observer and self ratings of symptom severity, underlining the validity of the results.

Published evidence on the efficacy of orally administered lavender oil preparations in psychiatric indications is sparse. Akhondzadeh *et al.* (Akhondzadeh *et al.*, 2003) compared the efficacy of *Lavandula angustifolia Mill.* tincture and imipramine in the treatment of 45 out-patients suffering from mild-to-moderate major depression. After 4 weeks of double-blind, randomized treatment the lavender oil preparation was determined to be less efficacious than imipramine, but the combination of imipramine and lavender oil was more efficacious than imipramine alone. In a double-blind, randomized study with 97 healthy volunteers Bradley *et al.* (Bradley *et al.*, 2009) presented anxiety provoking film clips after the individuals had ingested capsules with 100 or 200 µl of lavender oil or placebo. Compared with placebo individuals in the 200 µl condition exhibited lower state anxiety, galvanic skin response and heart rate as well as increased heart rate variation. The investigators interpreted the results to indicate an anxiolytic effect under conditions of low anxiety. Furthermore, in an open-label trial without a control group Stange *et al.* (Stange *et al.*, 2007) exposed 50 patients with neurasthenia, post-traumatic stress disorder or somatization disorder for 3 months to 80 mg/day of the same Lavandula oil preparation used in this trial. Using the State Trait Anxiety Inventory (Kendall *et al.*, 1976), von Zerssen's Depression Scale (von Zerssen *et al.*, 1974) and a sleep diary for assessment, state and trait anxiety as well as depression were reduced and efficiency of sleep was improved significantly. Although these trials indicate a potential beneficial effect of orally administered lavender oil preparations in psychiatric conditions, their external validity is limited by small sample sizes and methodological restrictions. Thus our trial was the first to show the anxiolytic efficacy of a well-defined, orally administered Lavandula oil preparation in a major psychiatric indication.

There have been considerable advances regarding the tolerability of anxiolytic drugs. For example, second-generation antidepressants like SSRIs that are increasingly used for treating anxiety disorder, have lessened the side-effect burden of anxiolytic drug therapy considerably as they are devoid of many of the well-known and partly serious side effects and paradoxical effects of benzodiazepines or tranquilizers (Masand and Gupta, 2003; Starcevic, 2005). However, effects like sedation and fatigue are still quite common and are sometimes accompanied by 'typical SSRI side effects' like gastrointestinal disturbances, agitation or insomnia (Preskorn, 1995; Trindade *et al.*, 1998), or by phenomena like weight gain and sexual dysfunction (Fava *et al.*, 2000; Hirschfeld and Vornik, 2004; Nelson *et al.*, 2006). In this trial, however, silexan and placebo showed a similar incidence and profile of AEs during the double-blind treatment period, and specific adverse reactions to the herbal essence were not observed.

Considering the herbal drug's efficacy showed in this trial silexan may be an effective treatment option in anxiety disorder NOS without compromising the patients' quality of life or social and professional functioning.

Conclusion

This study was performed to investigate the anxiolytic efficacy of the new oral lavender oil capsule preparation silexan in patients suffering from 'subsyndromal' anxiety disorder associated with disturbed sleep. The results demonstrate that Lavandula oil preparation administered orally at a dose of 80 mg/day is both efficacious and safe for relief of anxiety disorder NOS. The drug was determined to have a meaningful anxiolytic effect and to alleviate anxiety related disturbances of sleep while improving the physical and mental well-being. Taking into account that the tolerability of the herbal extract was on one level with placebo, the absence of unwanted sedative effects and the convenient once daily administration of silexan may emerge as a gentle therapeutic alternative in the treatment of anxiety.

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