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A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder

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ABSTRACT

Generalized and persistent anxiety, accompanied by nervousness and other symptoms (Generalised Anxiety Disorder, GAD) is frequent in the general population and leads to benzodiazepine usage. Unfortunately, these substances induce sedation and have a high potential for drug abuse, and there is thus a need for alternatives.

As the anxiolytic properties of lavender have already been demonstrated in pharmacological studies and small-scale clinical trials, it was postulated that lavender has a positive effect in GAD. A controlled clinical study was then performed to evaluate the efficacy of silexan, a new oral lavender oil capsule preparation, versus a benzodiazepine.

In this study, the efficacy of a 6-week-intake of silexan compared to lorazepam was investigated in adults with GAD. The primary target variable was the change in the Hamilton Anxiety Rating Scale (HAM-A-total score) as an objective measurement of the severity of anxiety between baseline and week 6. The results suggest that silexan effectively ameliorates generalized anxiety comparable to a common benzodiazepine (lorazepam). The mean of the HAM-A-total score decreased clearly and to a similar extent in both groups (by 11.3 ± 6.7 points (45%) in the silexan group and by 11.6 ± 6.6 points (46%) in the lorazepam group, from 25 ± 4 points at baseline in both groups). During the active treatment period, the two HAM-A subscores "somatic anxiety" (HAM-A subscore I) and "psychic anxiety" (HAM-A subscore II) also decreased clearly and to a similar extent in both groups.

The changes in other subscores measured during the study, such as the SAS (Self–rating Anxiety Scale), PSWQ-PW (Penn State Worry Questionnaire), SF 36 Health survey Questionnaire and Clinical Global Impressions of severity of disorder (CGI item 1, CGI item 2, CGI item 3), and the results of the sleep diary demonstrated comparable positive effects of the two compounds.

In conclusion, our results demonstrate that silexan is as effective as lorazepam in adults with GAD. The safety of silexan was also demonstrated. Since lavender oil showed no sedative effects in our study and has no potential for drug abuse, silexan appears to be an effective and well tolerated alternative to benzodiazepines for amelioration of generalised anxiety.

Introduction

Flowers of different species of lavender have been known for their wide therapeutic use for centuries. The main constituents of lavender oil are linalool, linalyl acetate, 1.8-cineole, β-ocimene, terpinen-4-ol and camphor (corresponding to GC chromatogram of lavender oil, European Pharmacopoeia 4th edition, 2002). The monograph in the Ph. Eur. 2002 describes a capillary gaschromatographic method and demands for the main terpenoids linalool, linalylacetate and terpinen-4-ol the %-values which must be in the range of 20.0-45.0, 25.0-46.0 and 1.2-6.0 respectively. These constituents can vary significantly in different oils.

The pure oil is most often used in aromatherapy and massage (Buchbauer et al. 1991). Despite its popularity and long tradition of use, only recently scientifically-based investigations into the biological activity of the various Lavandula species have been undertaken to a greater extent.

Small-scale studies have indicated that people with anxiety disorders might benefit from lavender massage. Lavender is able to decrease anxiety measured by the Hamilton rating scale (Itai et al. 2000) and can increase mood scores (Walsh and Wilson 1999). In another clinical study on 122 patients in a hospital intensive care

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unit, those subjects who received aromatherapy massage with Lavandula angustifolia oil reported a significant improvement in their perceived anxiety compared to patients with no aromatherapy (Dunn et al. 1995). A possible antidepressant effect of lavender has been investigated in smaller clinical trials (Diego et al. 1998; Vernet-Maury et al. 1999). However, no data on a lavender oil capsule formulation for oral application have been available until now.

Patients with a Generalised Anxiety Disorder (GAD, according to DSM-IV (300.02), ICD-10: F41.1) can experience excessive anxiety and worry associated with the stresses of everyday life. Most cases of GAD begin in childhood and can lead – without treatment – to a chronic condition, with fluctuating symptoms, often exacerbated by stressful life events (National Health Committee 1998; Wittchen and Hoyer 2001).

Treatment of GAD can be divided into psychotherapies and medicinal treatment. Pharmacotherapy is usually in the form of benzodiazepines, buspirone or antidepressants (Gliatto 2000).

Lorazepam is one of the common benzodiazepines and it acts on the gamma-aminobutyric acid (GABA)/benzodiazepine receptor complex. It suppresses activity in many limbic and other brain areas involved in anxiogenesis. The rapid onset of action is one of the advantages of the benzodiazepines, particularly in relieving the somatic symptoms of GAD. However, the benefits of short-term treatment are outweighed by the risks during long-term use of the substances (Tyrer and Murphy 1987). The disadvantages of taking benzodiazepines include a high risk of abuse or dependence, sedative effects, secondary symptoms of depression, psychomotor and cognitive impairment (Drug Monograph, 1995–2003). Withdrawal syndromes can occur during cessation after long term use.

Silexan[1] contains a quality-selected, well-defined preparation from *Lavandula angustifolia* in an immediate release capsule. Silexan acts via the $GABA_A$ receptors (Aoshima and Hamamoto 1999), and pre-clinical data have suggested that it may have anxiolytic and antidepressant potential (Schwabe internal pharmacological reports, unpublished).

The aim of this study was to investigate the therapeutic efficacy and tolerability of silexan[1] compared to lorazepam in the treatment of patients with GAD. This multi-centre, double-blind, randomised study with 2 parallel treatment groups was conducted by general practitioners.

Materials and methods

Subjects and study design

The study protocol was approved by an independent ethics committee (Ethikkommission der Landesärztekammer Baden-Württemberg, Stuttgart, Germany) and all subjects gave their written informed consent. The study was performed according to legal requirements and (ICH) GCP guidelines.

In this study, patients (18 to 65 years) with a primary diagnosis of generalised anxiety disorder (GAD) according to DSM-IV (300.02) and outpatient treatment by a general practitioner were selected. In order to be eligible for study inclusion, all patients were required to have a HAM-A total score $\geq$ 18 *and* Item 1 "anxious mood" $\geq$ 2 *and* Item 2 "tension" $\geq$ 2.

During the one-week screening phase, all patients received placebo to ensure wash-out of any other drugs. Patients with a decrease of 25% or more of the HAM-A total score during this phase were to be excluded. Only patients who met the inclusion criteria were admitted to the treatment period.

During the 6 weeks of the double blind randomized treatment phase, patients received either 1 × 1 capsule filled with 80 mg silexan (SMC 7563, batch no. 0200202) *and* 1 × 1 capsule filled with lorazepam placebo (SMC 9059P, batch no. 0200203/0200301), representing the silexan group, or 1 × 1 capsule of 0.5 mg lorazepam (SMC 9059, batch no. 0200204) *and* 1 × 1 capsule filled with silexan placebo (SMC 7563P, batch no. 0200201), representing the lorazepam group.

Silexan is an essential oil produced from Lavandula angustifolia flowers by steam distillation. As a basic requirement, it complies with the monograph Lavender oil of the European Pharmacopeia with respect to all quality parameters. In addition, silexan exceeds the quality definition of the pharmacopoeial monograpph with respect to items that are important for efficacy and tolerability due to specific improvements in relevant steps of the manufacturing process. The uniformity of the specific composition of Silexan is warranted by continuous quality controls.

The random code was generated using a validated computer program.

The eligibility procedures were undertaken on the day of screening; efficacy assessments of primary and secondary outcome variables as well as of safety parameters were carried out at baseline, weeks 1, 2, 4 and 6, and after the discontinuation phase at week 8.

The discontinuation phase was of 2 weeks' duration (day 43 – day 56). On day 43, 45, 47, 50 and 53, patients received either 1 × 1 capsule filled with 80 mg silexan (SMC 7563, batch no. 0200202) *and* 1 × 1 capsule filled with lorazepam placebo (SMC 9059P, batch no. 0200203/0200301) in the silexan group, or 1 × 1 capsule of 0.5 mg lorazepam (SMC 9059, batch no. 0200204) *and* 1 × 1 capsule filled with silexan placebo (SMC 7563P, batch no. 0200201) in the lorazepam group. On the other days, both groups received one capsule of silexan placebo (SMC 7563P, batch no. 0200201) and one capsule filled with lorazepam placebo (SMC 9059P, batch no. 0200203/0200301) per day.

Methods

Statistical analysis

The primary target variable for the analysis of the therapeutic equivalence of silexan and lorazepam was the change in HAM-A total score between baseline and week 6.

The two therapies were compared by looking at the observed difference between the treamtment groups and the two-sided 90% confidence intervals for the difference of expected values.

The primary analysis was based on the full analysis set. Furthermore, a per protocol analysis was performed which included only patients without major protocol violations.

Evaluation of the primary and secondary efficacy variables

The efficacy assessments from baseline to week 6 were based on the Hamilton Anxiety Rating Scale (HAM-A) as an objective measure of the severity of anxiety symptoms. The change in score was evaluated as the primary efficacy parameter.

To compare the effects of silexan and lorazepam, responder and remission rates were assessed as secondary objectives. Response was defined as a reduction of at least 50% in HAM-A total score between baseline and the end of treatment. A HAM-A total score below 10 points at week 6 was defined as remission. In addition, the Clinical Global Impression (CGI) as an organised global assessment of severity (conducted by the investigator), the Zung's Self–rating Anxiety Scale (SAS) which measures how much a patient suffers from common anxiety symptoms, the Penn State Worry Questionnaire past week version total score (PSWQ-PW) as a measure of worry, the SF-36 Health Survey Questionnaire for documentation of quality of life and a Patient's Sleep Diary to

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

document the duration and quality of patients' night time sleep were evaluated as secondary efficacy variables. The data from the sleep diary, which were entered by the patients from baseline to week 8, were condensed to mean values for each week, and the intra-individual changes between week 1 and week 6 were calculated and compared between the treatment groups.

For the assessment of the safety of silexan and lorazepam, physical examinations were performed, and vital signs, 12-lead ECG and routine laboratory parameters measured. The incidence and intensity of adverse events, suspected cases and serious adverse events, as well as the incidence of clinically relevant abnormal laboratory values, were compared between the treatment groups.

After the active treatment phase, the discontinuation phase started by reducing the medication step by step for another 2 weeks. The patients' vital signs were checked once more after 8 weeks. Again, HAM-A, CGI, SAS and PSWQ and an adverse event recording were carried out to evaluate changes in the patients' mood status after reduction of the study medication.

Results

Subjects

A total of 78 male and female patients entered the study, 77 were randomised to groups (silexan: 40 patients, lorazepam: 37 patients) and received study medication (Fig. 1).

During the active treatment period, at least one measurement of the HAM-A was available for all 77 patients who entered the study. All these patients could be evaluated for efficacy and safety (full analysis set). A total of 59 (76.6%) patients of the full analysis set were female and 18 (23.4%) were male. They were aged 21–65 years, had a weight of 44–118 kg, and a height of 150–185 cm (range of both treatment groups).

The time from first diagnosis of GAD was 4.5 ± 5.0 years in the lavender oil group and 3.6 ± 4.0 years in the lorazepam group.

The per protocol set (including only patients without major protocol violations) consisted of 69 patients (silexan: 36; lorazepam: 33).

Therapeutic progress with silexan compared to lorazepam during 6 weeks of treatment

If not stated otherwise, the results of the full analysis set are reported. In both treatment groups, the mean of the HAM-A total score from baseline to week 6 (active treatment period) decreased clearly and to a similar extent. The HAM-A total score (full analysis set) was 25 ± 4 points in both treatment groups at baseline and decreased during the active treatment phase of 6 weeks by 11.3 ± 6.7 points in the silexan group and by 11.6 ± 6.6 points in the lorazepam group (Fig. 2). This was similar to the per protocol evaluation, where HAM-A total score decreased by 11.4 ± 6.4 points in the silexan group (baseline score: 25 ± 4 points) and by 11.3 ± 6.4 points in the lorazepam group (baseline score: 25 ± 4

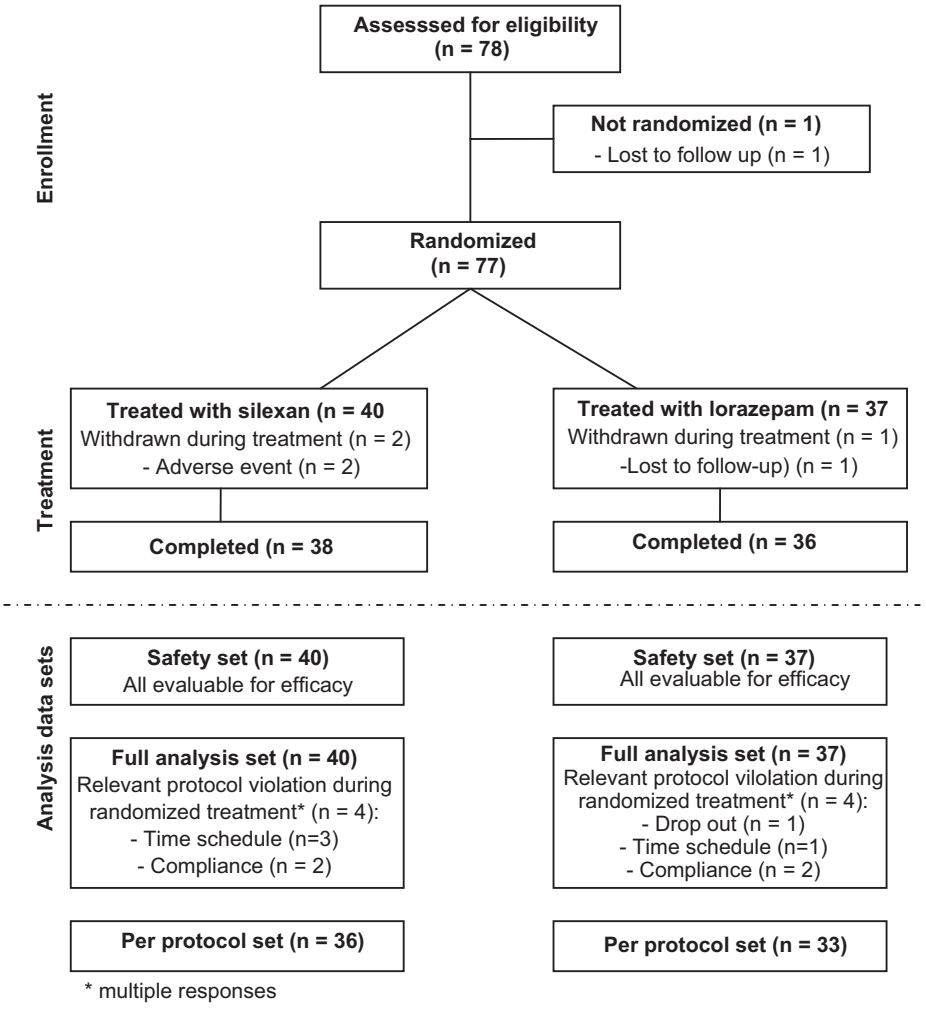

Fig. 1. Disposition of patients, analysis data sets.

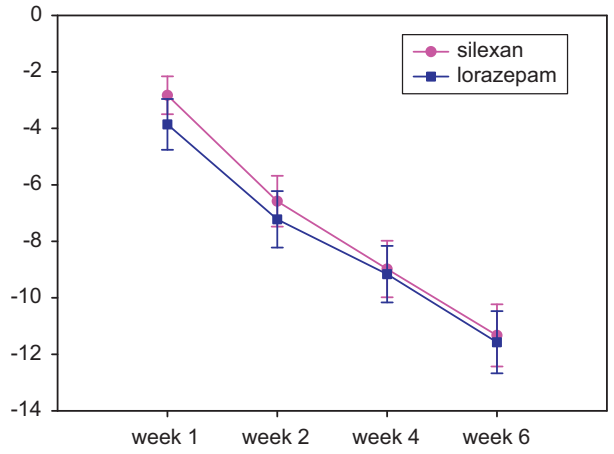

Fig. 2. Change (mean ± SEM) in HAM-A total score from baseline to week 6 during the active treatment period (full analysis set).

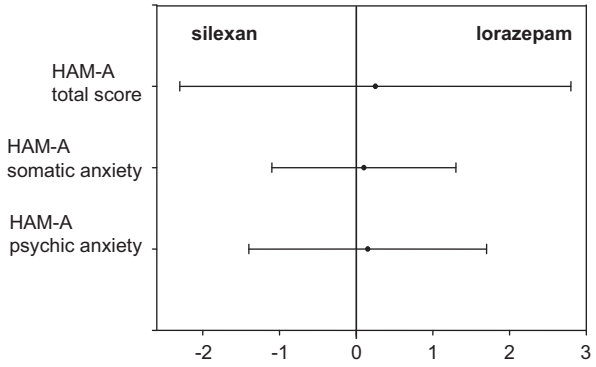

Fig. 3. Differences silexan – lorazepam, 90% confidence intervals and difference in means of HAM-A total score and HAM-A subscores (full analysis set).

points). Considering the changes of HAM-A total score between baseline and week 6 an inferiority of silexan compared to lorazepam of more than 2.8 points could be excluded (α=0.05, one-sided, 90%-confidence interval for the difference between the treatment groups (lavender oil – lorazepam) [−2.3; 2.8]). The 90% confidence intervals and the corresponding differences of means (full analysis set) for the primary test parameter are shown in Fig. 3. The results of efficacy analysis revealed comparable data for the two test groups. The HAM-A scores decreased similarly in both groups.

The comparison of responders and patients with remission in the treatment groups was a secondary objective of the study. During the active treatment period, the HAM-A total score of 21 (52.5%) patients in the silexan group and 15 (40.5%) patients in the lorazepam group decreased by at least 50%. These patients were judged to be responders. Assuming a margin of 7% for non-inferiority of lavender oil, a p-value of p=0.04 was determined for the responder rates with the Farrington Manning test. At the end of active treatment 16/40 patients in the silexan group (40%) and 10/37 patients in the lorazepam group (27%) showed remission. With a margin of 5% for non-inferiority of lavender oil, the p-value of the Farrington Manning test was p=0.04 for the rates of remission (Table 1).

The extent of somatic anxiety (HAM-A subscore I) at baseline was similar in both treatment groups (silexan 10.5 ± 2.5 points, lorazepam 10.8 ± 2.6 points) and lower than the extent of psychic anxiety (HAM-A subscore II; silexan 14.4 ± 2.1 points, lorazepam

Table 1
Analysis of responders and patients with remission. (Sample size, absolute (relative) frequency and one-sided p-value of the Farrington-Manning-test for non-inferiority of silexan compared to lorazepam)

	silexan	lorazepam	p-value
Full analysis set			
Reduction of HAM-A total score ≥ 50% by week 6[1)]	21 (52.5%)	15 (40.5%)	0.04
HAM-A-total score < 10 points at week 6[2)]	16 (40%)	10 (27%)	0.04
Per protocol set			
Reduction of HAM-A total score ≥ 50% by week 6[1)]	19 (52.7%)	13 (39.4%)	0.04
HAM-A-total score < 10 points at week 6[2)]	14 (38.9%)	8 (24.2%)	0.03

[1)] Margin for non-inferiority is a difference of 7%.
[2)] Margin for non-inferiority is a difference of 5%.

14.0 ± 2.0 points). During the active treatment period, both HAM-A subscores decreased clearly and to a similar extent in the two treatment groups. In the lavender oil group, psychic anxiety decreased by 6.9 ± 4.0 points, in the lorazepam group by 7.1 ± 4.3 points. Somatic anxiety decreased by 4.4 ± 3.3 points in the silexan group and by 4.5 ± 3.2 points in the lorazepam group.

The evaluation of the PSWQ-PW-total score showed a clear improvement during the active treatment period. At baseline the total score of the PSWQ-PW was 61.4 ± 11.3 points in the silexan group and 62.2 ± 12.2 points in the lorazepam group. It improved during the 6 weeks of treatment by 14.5 ± 17.8 points in the silexan group and by 16.6 ± 15.1 points in the lorazepam group.

The SAS-total score decreased clearly and to a similar extent in both treatment groups: the baseline value for silexan was 61.4 ± 6.6 and it improved by 14.8 ± 11.4 points. In the lorazepam group the SAS score at baseline was 61.5 ± 5.5 points and it improved by 14.4 ± 8.5 points.

The SF-36 mental health score at baseline was slightly higher in the silexan group (39.9 ± 15.9 points) than in the lorazepam group (36.5 ± 13.0 points), while the SF-36 physical health score was similar in both groups (silexan group: 59.5 ± 19.1 points, lorazepam group: 58.6 ± 20.5 points). Both SF-36 subscores increased clearly in the two treatment groups during the active treatment period (mental health: 21.2 ± 18.6 points silexangroup, 24.3 ± 18.7 lorazepam group; physical health: 12.5 ± 17.4 silexan group, 16.9 ± 18.9 lorazepam group).

At baseline, most of the patients were rated as moderately or markedly ill in CGI, item 1 (silexan group: 36 (90%), lorazepam group: 36 (97.4%)). After 6 weeks of active treatment, 24 patients (60%) treated with silexan were at the most mildly ill compared to 19 (51.3%) patients in the reference group. By the end of treatment, 28 (70%) patients of the silexan group and 19 (51.4%) patients treated with lorazepam were much or very much improved as rated by item 2 of CGI. Therapeutic efficacy of the study medication (item 3 of CGI) was assessed to be moderate or very good for 32 (80%) patients treated with silexan and 19 (51.3%) patients treated with lorazepam.

Evaluation of the sleep diary revealed that the latency to fall asleep in week 1 was higher in the lorazepam group (47 ± 73.1 min) than in the lavender oil group (30.2 ± 22.3 min). During the active treatment period, the latency to fall asleep decreased by 16.3 ± 70.8 min in the lorazepam group and by 3.9 ± 18.7 min in the silexan group. In contrast, the waking up duration in week 1 was slightly higher in the silexan group (33.4 ± 35.5 min) than in the reference group (26.5 ± 27.2 min),

and decreased during the treatment period by 12.2 ± 30 min in the silexan group and 3.7 ± 20.7 min in the reference group. In both treatment groups, the total sleep time was prolonged during the active treatment period (week 1: 405 ± 62.9 min in the silexan group, 397.4 ± 75.8 min in the lorazepam group) giving an improvement of 27 ± 55.6 min (silexan group) and 20.4 ± 59 min (lorazepam group). As a consequence, the total sleep time during the whole investigation period was also prolonged: By 22 ± 55.9 min in the silexan group and 15.7 ± 59 min in the lorazepam group. Other parameters assessed in the sleep diary changed only slightly in the two treatment groups. Analysis of the per-protocol set supported the results of the full analysis set.

In patients who participated in the discontinuation phase (silexan group: n=38, lorazepam group, n=35), a reduction in the HAM-A-total score of 13.5 ± 5.7 and 11.7 ± 7.7 points, respectively, was found over the whole treatment phase (baseline to week 8). Results of the full-analysis set were supported by analysis of the per-protocol set.

Safety evaluation

No serious adverse events occurred during the study. During the screening period, 5 patients suffered from 6 adverse events. A total of 20 patients treated with silexan suffered from 26 adverse events compared to 18 patients (19 adverse events) treated with lorazepam. In the silexan group, a causal relationship to the study medication could not be ruled out for 11 adverse events (10 patients), and 7 adverse events (7 patients) in the lorazepam group were judged to be potentially related to the study medication. Nine of the eleven adverse events that occurred in the silexan group were gastrointestinal disorders (nausea: 4 adverse events, eructation/breath odour: 3 adverse events, dyspepsia: 2 adverse events). In the reference group, 1 patient suffered from nausea and 6 patients suffered from fatigue, which is a known adverse drug reaction of lorazepam.

Discussion

The results from the multi-centre, double-blind, randomised phase III study demonstrate that silexan is not less effective than lorazepam in the treatment of patients with generalized anxiety disorder. This can be concluded by comparing the primary outcome variable, the reduction of HAM-A total score between the treatment groups. Responder rates of 52.5% for silexan and 40.5% for lorazepam, as well as remission rates of 40% versus 27%, respectively, demonstrate the clinical relevance of the observed effect. Treatment with silexan thus appears to be at least as effective as one of the most common benzodiazepines.

The positive finding in the primary outcome variable is supported by the analysis of the secondary outcome variables. A clear and similar decrease in the HAM-A subscores (psychic and somatic anxiety) and the SAS-total score, and an improvement in the PSWQ-PW-total score were found in both treatment groups and in the different analysis data sets during the 6 weeks of active treatment. Both SF-36 subscores (mental health score and physical health score) increased clearly during the active treatment period in both groups. Likewise, the clinical global impression (CGI, item 1-3) of most patients improved by the end of the study (at week 6) in the two treatment groups. The severity of the illness changed to at most mild, the anxiety disorder was much or very much improved and the therapeutic efficacy was assessed to be moderate or very good after 6 weeks of treatment.

As already shown in former studies, lavender oil has, in addition to the anxiolytic properties, sleep-inducing properties (Wolfe and Herzberg 1996; Hardy et al. 1995) without daytime sedating effects. In our clinical study, the tested substances also improved the patients' sleeping behaviour. The total sleep time of both treatment groups could be prolonged. The latency to fall asleep and the waking up duration decreased during the 6 weeks of treatment.

It should be pointed out that the reduction in HAM-A-total score could be extended during the discontinuation phase in both treatment groups. This means a similar reduction of the primary target parameter after 8 weeks of treatment, and it demonstrates a continuation of the anxiolytic effect of silexan even after reducing the drug dose.

On internal use of the volatile lavender oil, nausea (Atanassova-Shopova and Roussinov 1970) and drowsiness after excessive intake have been reported (Leung and Foster 1996). In this study, the adverse events of silexan were mostly gastrointestinal disorders and no serious adverse events occurred in the silexan group. This demonstrates the good tolerability of the new lavender oil capsule preparation. Owing to the favourable safety profile of lavender oil at the recommended doses (Drug Monograph 1984), the risk-benefit ratio for silexan appears to be very good. In the lorazepam group 6 patients suffered from fatigue, a symptom of the sedative properties of the benzodiazepine or possibly a kind of a hangover effect.

In conclusion, the results of this study demonstrate that administration of silexan 80 mg capsule formulation is as effective as and comparable to lorazepam 0.5 mg in adults with GAD. The primary, and nearly all the secondary variables, which measured anxiety, worry, severity of illness and sleep disturbance, improved clearly and to a similar extent in both groups. Global improvement and efficacy after 6 weeks of treatment were assessed to be even better in the silexan group than in the lorazepam group. Furthermore, the safety of the new drug formulation silexan was shown. Since lavender oil has no potential for drug abuse and causes no hangover effects silexan appears to be an effective and well-tolerated alternative to benzodiazepines for amelioration of generalised anxiety.

Conflict of interest:

Prof. H. Woelk has served as a consultant for Dr. Willlmar Schwabe GmbH & Co. KG, the sponsor of the submitted study.

S. Schläfke is an employee of Dr. Willlmar Schwabe GmbH & Co. KG.

References

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

Atanassova-Shopova, S., Roussinov, K.S., 1970. On certain central neurotropic effects of lavender essential oil. Izv. Inst. Fiziol. 13, 69–77.

Buchbauer, G., Jirovetz, L., Jäger, W., Dietrich, H., Plank, Ch., Karamat, E., 1991. Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation. Z. Naturforsch. 46c, 1067–1072.

Diego, M., Jones, N., et al., 1998. Aromatherapy positively affects mood, EEG patterns of math computations. Int. J. Neurosci. 96, 217–224.

Drug Monograph (Germany): Lavendulae flos. Lavendelblüten. BAnz vom 5.12.1984 und 13.03.1990.

Drug Monograph Lorazepam; Internet Mental Health (Canada) copyright© 1995-2003 by Phillip W. Long, URL: http://www.mentalhealth.com/drug/p30-a04.html (accessed Sept. 23 2008).

Dunn, C., Sleep, J., Collett, D., 1995. Sensing an improvement: an experimental study to evaluate the use of aromatherapy, massage and periods of rest in an intensive care unit. J. Adv. Nurs. 21, 34–40.

Gliatto, M.F., 2000. Generalized anxiety disorder. Am. Fam. Phys. 62, 1591–1600.

Hardy, M., Kirk-Smith, M.D., Stretch, D.D., 1995. Replacement of drug treatment for insomnia by ambient odor. Lancet.

Itai, T., Amayasu, H., Kuribayashi, M., et al., 2000. Psychological effects of aromatherapy on chronic hemodialysis patients. Psychiatry Clin. Neurosci. 54, 393–397.

Leung, A.Y., Foster, S., 1996. Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics. John Wiley & Sons, New York pp. 339–342.

National Health Committee (United Kingdom) 1998; Guidelines for Assessing and Treating Anxiety Disorders.

Tyrer, P., Murphy, S., 1987. The place of benzodiazepines in psychiatric practice. Br. J. Psychiatry 151, 719–723.

Vernet-Maury, E., Alaoui-Ismaili, O., Dittmar, A., Delhomme, G., Chanel, J., 1999. Basic emotions induced by odorants: a new approach based on autonomic pattern results. J. Auton. Nerv. Syst. 75, 176–183.

Walsh, E., Wilson, C., 1999. Complementary therapies in long-stay neurology in-patient settings. Nurs. Stand 13, 32–35.

Wittchen, H.U., Hoyer, J., 2001. Generalized anxiety disorder: nature and course. J. Clin. Psychiatry 62 (Suppl. 11), S21–S30.

Wolfe, N., Herzberg, J., 1996. Can aromatherapy oils promote sleep in severely demented patients?. Int. J. Geriatric Psychiatry 11, 926–927.