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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

H. Woelk [a], S. Schläfke [b]

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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 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.

Section snippets

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 …

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 …

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 …

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. …

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