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File: ■ Lavender (*Lavandula angustifolia*, Lamiaceae)
■ Anxiety
■ Depression
■ Silexan®

HC 021653-552

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RE: Oral Lavender Oil Reduces Anxiety and Depression in Patients with Mixed Anxiety and Depressive Disorder (MADD)

Kasper S, Volz H-P, Dienel A, Schläfke S. Efficacy of Silexan in mixed anxiety-depression – A randomized, placebo-controlled trial. *Eur Neuropsychopharmacol*. February 2016;26(2):331-340.

In some cases, patients present to the doctor with both anxiety and depression, but neither condition is dominant, and neither can be classified as generalized anxiety disorder (GAD) or as a major depressive episode. The World Health Organization has included Mixed Anxiety and Depressive Disorder (MADD) as a diagnosis for such patients in the *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision (ICD-10). Silexan® (Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany) is the patented active substance in Lasea® (Dr. Willmar Schwabe GmbH & Co. KG), which contains 80 mg of lavender (*Lavandula angustifolia*, Lamiaceae) flower oil in each capsule. Randomized, double-blind, placebo-controlled trials have shown that Silexan is an effective anxiolytic in patients with GAD or subsyndromal anxiety disorder. Secondary outcome measures used in these trials suggest that Silexan may also have an antidepressant effect. The purpose of this randomized, double-blind, placebo-controlled study was to evaluate the efficacy and safety of Silexan in patients with MADD.

Outpatients (n = 318; aged 18-65 years), diagnosed with MADD according to the ICD-10, participated in this study conducted at 35 psychiatric practices in Germany between November 2012 and February 2014. Included patients had ≥ 18 points on the Hamilton Anxiety Rating Scale (HAMA), with ≥ 2 points (indicating ≥ moderate symptom intensity) for HAMA items of "anxious mood" and "depressed mood" at inclusion and baseline. Patients were excluded if they had any previous suicidal attempts or clear auto-aggressive behavior, ≥ 2 points on the item of "suicidal thoughts" on the Montgomery Åsberg Depression Rating Scale (MADRS), other clinically relevant psychiatric or neurological diagnoses within the 6 months preceding randomization, substance abuse, or used psychotropic drugs within the 30 days preceding randomization. Concomitant psychotropic co-medication and psychotherapy were not permitted during the study.

Patients received either 80 mg/day Silexan or placebo for 70 days. Silexan complies with the lavender oil monograph of the *European Pharmacopoeia*, and the dosage was established in accordance with the German marketing authorization for the product. The placebo capsules were scented with 1/1000 of the amount of lavender oil in the Silexan capsules to match the smell of Silexan (no other placebo contents were described).

The primary efficacy measure was the change in the investigator-rated HAMA and MADRS total scores from baseline to study end (10 weeks). For HAMA and MADRS, incidence of a "favourable treatment response" (50% decrease in total score) and incidence of remission (< 10 points on HAMA and ≤ 10 points on MADRS at study end) were secondary outcome measures. Other secondary outcome measures were the self-rated State-Trait Anxiety Inventory (STAI), Hospital Anxiety and Depression Scale (HADS), and Sheehan Disability Scale (SDS); the investigator-rated Clinical Global Impressions scale (CGI) and Short Form Health Survey (SF-36); adverse events (AEs); and safety parameters. For the CGI, a clinically relevant response was predefined as the number of patients with a reduction of illness severity of at least 2 categories (CGI item 1) and the number of patients assessed to be much or very much improved (CGI item 2). HAMA, MADRS, HADS, and STAI were assessed at baseline and weeks 1, 2, 4, 7, and 10; CGI item 1, SDS, and SF-36 were assessed at baseline and week 10; and CGI item 2 was assessed only at week 10.

The majority (more than two-thirds) of the patients were women, and all but 2 patients were Caucasian. There were no significant differences between groups in demographic data or outcome measures at baseline. Based on CGI assessments, half of the patients in each group were at least moderately ill at baseline. Compliance was 99.6% in the Silexan group and 99.4% in the placebo group; 1 patient in the Silexan group and 5 patients in the placebo group were excluded from the per-protocol analysis due to unacceptable compliance. The frequency of AEs was similar between groups. Eructation (belching) was the only AE that occurred in the Silexan group markedly more frequently than in the placebo group (10.0% vs. 0%, respectively) and was considered potentially related to the treatment.

Anxiolytic Effect

The Silexan group had a significantly greater decrease in HAMA total scores than the placebo group at study end ($P = 0.008$, one-sided, analysis of covariance [ANCOVA] with treatment and centers as factors and the HAMA total score at baseline as covariate). Silexan showed a statistically significant advantage over placebo from week 4 until treatment end. HAMA subscores indicated Silexan had a significant effect on both somatic and psychic anxiety ($P = 0.03$ for both subscales, two-sided t-tests). Responder and remitter rates were higher in the Silexan group (41.5% and 34.6%, respectively) than in the placebo group (34.6% and 28.8%, respectively). The Silexan group showed better improvement in anxiety than the placebo group, according to the STAI and HADS anxiety subscore (data not shown).

Antidepressant Effect

The Silexan group had a significantly greater decrease in MADRS total score than the placebo group at study end ($P < 0.001$, one-sided, ANCOVA with treatment and centers as factors and the HAMA total score at baseline as covariate). Silexan showed a statistically significant advantage over placebo from week 4 until treatment end. Responder rates were higher in the Silexan group (40.3%) than in the placebo group

(32.1%), and significantly more patients in the Silexan group (46.5%) than the placebo group (34.0%) were in remission (P = 0.02, two-sided chi-square test). HADS depression subscore decreased in both groups.

Subgroup analyses of HAMA and MADRS scores revealed that patients with more severe symptoms at baseline had greater improvement with Silexan.

Significantly more patients in the Silexan group than the placebo group had a reduction of illness severity of at least 2 categories on the CGI (P < 0.01, two-sided chi-square test), and the number of patients assessed as much or very much improved on the CGI was significantly greater in the Silexan group (P < 0.01, two-sided chi-square test). Improvements in daily living skills were significantly more pronounced in the Silexan group compared with the placebo group based on SDS total score (P < 0.01, two-sided t-test) and all SDS subscores (P < 0.05, two-sided t-tests). SF-36 physical and mental health total scores were significantly more improved in the Silexan group than in the placebo group (P = 0.01 and P < 0.01, respectively, two-sided t-tests). The greatest benefits were observed in improving general health, vitality, role emotional, mental health, social functioning, and bodily pain (P ≤ 0.05 for all, two-sided t-tests).

The authors conclude that "in patients suffering from MADD according to ICD-10 criteria, Silexan has an anxiolytic and antidepressant effect that leads to an improvement of impaired daily living skills and health related quality of life and it was very well tolerated." The pre-determined standards for clinical relevance based on the CGI were met, indicating that Silexan had significant benefits in terms of reducing illness severity and global improvement. The homogenous ethnicity and age of the study population, and the preponderance of female patients, may limit the generalization of the results, as it is not clear whether this sample population was truly representative of patients diagnosed with MADD. The degree to which illness severity at baseline may impact the efficacy of Silexan is unclear and should be explored in future studies. The study should be repeated with other populations. The manufacturer of Silexan, Dr. Willmar Schwabe GmbH & Co. KG, funded the study. Two of the authors are employed by Dr. Willmar Schwabe GmbH & Co. KG (Dienel and Schläfke); the other 2 authors (Kasper and Volz) have served as consultants, on advisory boards, and/or on speakers' bureaus for Dr. Willmar Schwabe GmbH & Co. KG.

This article fulfilled all of the Consolidated Standards of Reporting Trials (CONSORT) of herbal interventions criteria very well, with detailed reporting of all items except the chemical characterization of Silexan.

—Heather S. Oliff, PhD

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