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File: ■ Lavender (*Lavandula angustifolia*)
■ Generalized Anxiety Disorder
■ Silexan™

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RE: Oral Lavender Oil Product Effective and Safe in Generalized Anxiety Disorder

Kasper S, Gastpar M, Müller WE, et al. Lavender oil preparation Silexan is effective in generalized anxiety disorder – a randomized, double-blind comparison to placebo and paroxetine. *Int J Neuropsychopharmacol.* January 23, 2014:1-11. [epub ahead of print]. doi: 10.1017/S1461145714000017.

Generalized anxiety disorder (GAD) can be very disruptive, and is characterized by anxiety along with restlessness, fatigue, concentration problems, tension, irritability, and/or sleep problems, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*). Lavender (*Lavandula angustifolia*) has been used for mental health problems,[1] and the product used in this study has been shown in clinical trials to reduce symptoms of anxiety.[2,3] This randomized, double-blind, placebo-controlled trial investigated 2 dosages of an oral lavender essential oil product (Silexan™; Dr. Willmar Schwabe GmbH & Co.; Karlsruhe, Germany) in comparison with the selective serotonin reuptake inhibitor paroxetine in patients diagnosed with GAD. Dr. Willmar Schwabe GmbH & Co. funded the study.

The primary outcome of this study was any effect of Silexan consumption on GAD in comparison with placebo, as measured by Hamilton Anxiety Scale (HAMA) total score. This scale assesses 14 symptoms of anxiety through a scale ranging from 0 (symptom absent) to 4 (symptom severe). The secondary outcome was the effect of Silexan consumption as compared with paroxetine. Included patients were initially screened and underwent a period of washout (3-7 days) before the study. Treatment was given for 10 weeks, with measurements of safety and efficacy at 2, 4, 6, 8, and 10 weeks. A week of "down-titration" was done following the study to account for any withdrawal problems caused by paroxetine.

Both male and female patients were enrolled from 57 general and psychiatric practices in Germany. Included patients were between 18 and 65 years old and diagnosed with GAD, as outlined in *DSM-IV-TR*. Included patients also had a HAMA score of ≥ 18, with scores ≥ 2 for anxious mood and tension symptoms, as well as ≤ 21 for psychic anxiety. The Covi Anxiety Scale (CAS) was also used, and included patients had a score of ≥ 9. Those with additional psychiatric illnesses were excluded, and other psychiatric medications were not allowed during the study or during the 30 days prior to the study.

Silexan is produced from steam-distilled fresh flowering tops of lavender and standardized to contain approximately 70% of the compounds linalool and linalyl acetate. Silexan was provided in either 80 or 160 mg doses, and paroxetine was given in capsules of 20 mg. The Silexan placebos were masked by containing 1/1,000 dilution of lavender oil (0.08 mg) per capsule, and patients consumed all capsules without chewing. Patients consumed 1 capsule of treatment and 1 placebo or 2 placebos daily. In the down-titration period, patients took treatments every other day with those in the Silexan groups taking only placebo.

Any change in HAMA total score after 10 weeks, or end of treatment for early withdrawals, were the primary outcomes. The main secondary outcome was a decrease in HAMA score of 50% or more, or a decrease in HAMA score of more than 10 points. Changes in scores from CAS, Hamilton Rating Scale for Depression (HAMD), and Clinical Global Impressions (CGI) scales were also secondary outcomes. Adverse events reports were spontaneous. Safety and efficacy were determined at baseline and weeks 2, 4, 6, 8, and 10.

In total, 616 patients were recruited with 539 randomly assigned into treatment or placebo groups; 536 patients received treatment: 128 in the 160 mg/d Silexan group, 135 in the 80 mg/d Silexan group, 137 in the paroxetine group, and 136 in the placebo group. [Note: It is not mentioned why 3 patients did not start treatment.] At the start of the study, the majority of patients (60-74% in each group) also had vascular, musculoskeletal, metabolic, or nutritional health problems. The average time period that patients had GAD was 2.5 years, and current instances of GAD averaged about 1 year. All patients had HAMA scores clearly over 18 at baseline, with the CGI item 1 scores pointing to "moderate" or "marked" GAD severity. Patients in the 160 mg/d Silexan group showed significantly higher CAS and Sheehan Disability Scale (SDS) scores (P=0.03 and 0.01, respectively), as well as a significantly less SF-36 mental health score (a health survey, P=0.02) as compared to placebo at baseline.

For the main study analysis, the full analysis set (FAS) was used, consisting of all patients randomly assigned minus those without efficacy data after the start of the study (121 patients in the 160 mg/d Silexan group, 135 in the 80 mg/d Silexan group, 132 in the paroxetine group, and 135 in the placebo group). Patients were withdrawn from the study for adverse events (AEs), reversal of consent, efficacy problems, or loss to follow up.

According to the FAS analysis, after 4 weeks of the study and at all other later time points, consumption of 160 mg/d of Silexan resulted in a significantly greater change in HAMA score as compared to those in the placebo group ($P<0.01$). Also, after 6 weeks of treatment and all other later time points, those taking 80 mg/d of Silexan had a significantly greater change in HAMA scores as compared to the placebo (P=0.02). The change in HAMA scores in those taking paroxetine at week 6 approached significance as compared to those in the placebo group (P=0.06), but HAMA score changes were not significantly different from placebo thereafter.

A significantly greater percentage of patients in the 160 mg/d Silexan group showed an improvement in the HAMA score of ≥ 50% as compared to the placebo group (60.3% vs. 37.8%, $P<0.001$). This was also seen in those taking 80 mg/d of Silexan (51.9% vs. 37.8%, $P<0.05$). There were significantly more of those taking 160 mg/d of Silexan with

a HAMA score of < 10 as compared to those in the placebo group (46.3% vs. 29.6%, P<0.001). All treatment groups contained a greater percentage of patients classified as "much/very much improved" or "moderate/marked" therapeutic effect, according to the CGI, with the differences significant for both Silexan groups (P<0.001) and for the paroxetine group (P<0.01) as compared to those in the placebo group.

AEs were reported by 25.0% of those in the 160 mg/d Silexan group, 34.8% of those taking 80 mg/d of Silexan, 40.9% of those taking paroxetine, and 30.9% in the placebo group. The AEs consisted of gastrointestinal disorders, infections, and nervous system problems. No AEs associated with down-titration withdrawal were observed in any of the groups.

According to the HAMA scores, both dosages of Silexan are efficacious in treating GAD and were more efficacious than the dosage of paroxetine used in the study. Additionally, those taking Silexan had a similar incidence of AEs as compared to placebo, suggesting that the product is well tolerated. Despite these results, there are some weaknesses of this study. For example, it is unclear why the final analysis was done on the FAS group as opposed to the per protocol group, which would have accounted for all patients withdrawn from the study. Also, no biochemical markers of safety from the routine laboratory measurements were reported, and, aside from AEs reports, all data relied on questionnaires. Further clinical trials are necessary to confirm mechanisms of action behind the bioactivity reported here.

—Amy C. Keller, PhD

References

[1]Blumenthal M, Goldberg A, Brinckmann J, eds. *Herbal Medicine: Expanded Commission E Monographs*. Austin, TX: American Botanical Council; Newton, MA: Integrative Medicine Communications; 2000.

[2]Kasper S, Anghelescu IG, Dienel A. Efficacy of Silexan (WS® 1265) in patients with restlessness and sleep disturbances. In: Annual Congress of the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN). Berlin, Germany; 2010.

[3]Kasper S, Gastpar M, Müller WE, et al. 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*. September 2010;25(5):277-287.

The American Botanical Council has chosen not to include the original article.