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File: ■ Lavender (*Lavandula angustifolia*, Lamiaceae)
■ Restlessness
■ Sleep Disturbances

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RE: Oral Lavender Essential Oil Reduces Restlessness and Anxiety in Patients with Subthreshold Anxiety Disorders

Kasper S, Anghelescu I, Dienel A. Efficacy of orally administered Silexan in patients with anxiety-related restlessness and disturbed sleep – A randomized, placebo-controlled trial. *Eur Neuropsychopharmacol*. August 7, 2015; [epub ahead of print]. doi: 10.1016/j.euroneuro.2015.07.024.

Restlessness and sleep disturbances are among the symptoms of anxiety disorders. Patients with anxiety need a treatment that is calming but not sedating. Restlessness and disturbed sleep are the main indications for lavender (*Lavandula angustifolia*, Lamiaceae) flower essential oil. Silexan® (Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany) is a patented product containing 80 mg of standardized lavender flower essential oil in each soft gelatin capsule. Clinical studies show that Silexan produces anxiolysis in patients with generalized anxiety disorder (GAD) and subthreshold anxiety disorder. The purpose of this randomized, placebo-controlled, multicenter study was to evaluate the efficacy and tolerability of Silexan in patients with subthreshold anxiety disorder who suffer from restlessness and disturbed sleep.

The study was conducted at 17 general and psychiatric practices in Germany. Patients (n=170, aged 18-65 years) were included if they had restlessness and agitation according to the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10); ≥ 5 of 10 points on a visual analog scale of restlessness and agitation; substantial disease-related impairment of daily living; ≥ 18 points on the Hamilton Anxiety Rating Scale (HAMA); ≥ 2 points for HAMA items "Tension" and "Insomnia"; and disturbed sleep as confirmed with a score of ≥ 6 points on the Pittsburgh Sleep Quality Index (PSQI). Patients were excluded for the following reasons: HAMA total score decrease of ≥ 25% between study inclusion and baseline measurements; psychiatric or neurological disease diagnosis ≥ 6 months before study entry (except anxiety); depression; somatoform disorders; neurasthenia; personality disorder; primary insomnia; suicidal; substance abuse; taking psychotropic medication or muscle relaxants; and undergoing psychotherapy. During a 3- to 7-day screening/run-in period, all patients took 1 placebo capsule. After baseline assessment, patients received either placebo or Silexan 80 mg/day for 10 weeks. The placebo contained 1/1000 of the

amount of lavender oil found in Silexan to match the smell of Silexan. The primary outcome measure of anxiolytic effect was HAMA total score change; the primary outcome measure of sleep improvement was PSQI score change. The secondary outcome measures were the number of treatment responders and remitters, HAMA sub-scores, Zung Self-Rating Anxiety Scale (SAS), Clinical Global Impressions (CGI) observer rating scale, and the State Check (SC) self-check scale. Response to treatment was defined as ≥ 50% change from baseline to study end on the HAMA, and clinical remission (remitter) was defined as having a HAMA total score < 10 points at study end.

Baseline demographic characteristics were similar between groups. After randomization, the full analysis set (FAS) consisted of n=86 in the Silexan group and n=84 in the placebo group; the per-protocol (PP) analysis included n=73 in the Silexan group and n=65 in the placebo group. Exclusions from the PP analysis were comparable between the 2 groups except for non-compliance (n=8 placebo patients and n=0 Silexan patients).

Significant improvements in HAMA total score were observed in the Silexan group after 4 weeks of treatment, compared to placebo. After 10 weeks, the 12-point decrease in HAMA total score in the Silexan group was significantly greater than the 9.3-point decrease in the placebo group (P=0.03). The Silexan treatment effect was more pronounced in the PP analysis. Patients with more severe baseline HAMA total scores had greater Silexan-induced improvements. The number of responders in the Silexan group (48.8%) was significantly greater than the number (33.3%) in the placebo group (P=0.04); there was no significant difference between the 2 groups in the number of remitters. Compared with placebo, the number of patients reporting that they never, seldom, or sometimes felt restless on the SC scale significantly increased in the Silexan group (P=0.01). The CGI assessments also reflected greater improvements in the Silexan group compared to placebo. There was no significant difference between groups in the PSQI total score change, indicating that Silexan does not have a sedative effect. This finding is supported by the lack of adverse events (AEs) related to sedation.

The frequency of AEs was similar between groups, and there were no serious AEs in either group. In double-blinded assessment, 9 patients in the Silexan group and 4 patients in the placebo group had an AE in which a causal relationship to the treatment could not be excluded. All potentially related AEs in the Silexan group were gastrointestinal complaints. Overall, Silexan was well tolerated.

The authors conclude that this study not only confirms the anxiolytic effect of Silexan observed in other clinical trials but also shows it significantly reduces restlessness without causing sedation. Therefore, Silexan may be beneficial irrespective of whether the patient presents to the clinician with restlessness or anxiety. A limitation of the study is that there is no validated psychiatric scale for assessing restlessness, and the authors had to develop their own scale. The study was funded by the manufacturer of Silexan, Dr. Willmar Schwabe GmbH & Co. KG. The lead author (SK) has received funding from and served as a consultant to numerous pharmaceutical companies, including Dr. Willmar Schwabe; another author (AD) is employed by Dr. Willmar Schwabe.

—Heather S. Oliff, PhD

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