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FILE: ▪Kava
▪Anxiety
▪Benzodiazepines

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RE: Study of Kava in the Treatment of Anxiety

Malsch U, Kieser M. Efficacy of kava-kava in the treatment of non-psychotic anxiety, following pretreatment with benzodiazepines. *Psychopharmacology* 2001; 157:277-283.

In the midst of controversy over the safety of kava (*Piper methysticum*), research regarding its efficacy and safety for patients suffering from anxiety continues. An earlier clinical trial has shown the kava extract WS®1490 (Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany) to be equivalent to benzodiazepines in anxiolytic efficacy, without the sedative effects and adverse drug reactions frequently found with benzodiazepines. This article describes a prospective, randomized, placebo-controlled, double-blind study to assess the anxiolytic efficacy of WS®1490 compared to placebo in the context of benzodiazepine pretreatment. The study also sought to assess the potential of WS®1490 to reduce withdrawal symptoms from benzodiazepine therapy and effectively replace benzodiazepine.

Eligible subjects in this hospital-based clinical trial suffered from non-psychotic anxiety, tension, and restlessness resulting in social and work impairment. A minimum of 14 days of uninterrupted benzodiazepine treatment prior to the beginning of the study was required, as well as a medical indication for the discontinuation of such treatment in favor of another anxiolytic drug. During the 5-week double-blind treatment phase, subjects received either WS®1490 (n=20) or placebo (n=20). The daily dose was gradually increased from 50 mg to 300 mg per day during the first week, while the pre-existing benzodiazepine dose was steadily tapered off over the first 2 weeks. These adjustments were followed by 3 weeks of treatment with either WS®1490 or placebo alone. A 3-week follow-up phase served as a withdrawal trial with placebo for those patients whose scores had improved, while those whose scores had not changed or had deteriorated were given anxiolytic treatment at the discretion of the investigator. Primary outcome measures included scores on the Hamilton Anxiety Scale (HAMA), the "Befindlichkeits-Skala" (Bf-S – subjective well-being scale), and incidence of benzodiazepine withdrawal symptoms.

Subjects were well matched with regard to anthropometric and demographic characteristics as well as HAMA and Bf-S scores and length of pretreatment with benzodiazepines. Of the 40 original subjects, three participants (WS®1490:2; placebo:1) withdrew from the study prematurely due to benzodiazepine withdrawal symptoms. During the randomized treatment phase, the WS®1490 group showed a marked decrease in the HAMA score with obvious benefit after only one week of treatment, while there was no comparable improvement in the placebo group, whose HAMA scores varied around baseline. Results for

subjective well-being, as measured by the Bf-S score, were comparable to those described for the HAMA, with a difference of approximately 1.5 standard deviations between the treatment and placebo groups. The effectiveness of WS®1490 over placebo was statistically significant at treatment end. The incidence of benzodiazepine withdrawal symptoms, noted in 8 patients in the WS®1490 group and 10 in the placebo group, did not reach statistical significance. Secondary variables (the Erlangen Anxiety and Aggression Scale and the Clinical Global Impressions (CGI)) showed improvements with WS®1490 when compared to placebo.

During the follow-up phase, the 4 patients in the WS®1490 group and the 11 in the placebo group who did not show reduction in their HAMA total score during the double-blind trial were treated with anxiolytics. Patients who were treated successfully during the double-blind phase of the trial were given placebo during follow-up as a withdrawal trial. Out of the 18 patients in the WS®1490 group, 10 showed recurrence or persistence of the symptoms of anxiety disorder after discontinuation of WS®1490, interpreted as evidence for the efficacy of WS®1490. Nine of these 10 had improved during the double-blind phase of the trial. Five patients in the WS®1490 group and 10 in the placebo group reported adverse events, which the authors state were nonspecific and related to benzodiazepine withdrawal.

The authors conclude that the kava extract WS®1490 is significantly more effective than placebo in moderately severe, non-psychotic anxiety disorders. Importantly, patients treated with WS®1490 showed improvement in symptoms compared to the end of their benzodiazepine therapy, indicating that WS®1490 may be a more effective anxiolytic for some patients than benzodiazepine drugs. Mild withdrawal symptoms during the double-blind trial were more pronounced and more frequent in the placebo group than the WS®1490 group. No withdrawal symptoms from WS®1490 were seen at the end of the treatment phase.

The authors note that in addition to confirming the effect of the kava extract WS®1490, this study shows that further relief of many patients' symptoms could be achieved despite long previous treatment with benzodiazepines. Whether this is due to improved benefit from WS®1490 over benzodiazepines or from a benzodiazepine tolerance effect, they state that WS®1490 can be considered an effective and safe replacement for benzodiazepines in treatment of anxiety disorders. The authors suggest that since WS®1490 did not show any addictive properties in this study or other previous studies, it shows great potential for the long-term treatment in patients with a high risk of dependency.

— Diane S. Graves, MPH, RD

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