Is kava extract effective for treating anxiety?

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Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. *J Clin Psychopharmacol* 2000;20:84-9.

Research question

Is kava extract (*Piper methysticum*) more effective than placebo for treating patients with anxiety?

Type of article and design

Systematic review and meta-analysis.

Relevance to family physicians

Anxiety disorders affect the lives of one in every six Canadians.[1] Lifetime incidence of anxiety disorders in Ontario is up to 17% for men and 28% for women.[2] Anxiety disorders can adversely affect patients' day-to-day functioning, productivity, and quality of life and can lead to complications, such as depression and substance abuse. Just as depressive disorders were not mentioned by patients in the past, so anxiety is often not mentioned by patients now, because it is not viewed as a medical condition. Treating patients with anxiety nonetheless constitutes an important component of family physicians' practices.

Current treatment options for patients with anxiety include psychological interventions, such as cognitive behavioural therapy, and drug therapy. Limited resources and time constraints often mean that psychological interventions are not readily available and feasible for patients with anxiety. Although several pharmacologic agents, including benzodiazepines, buspirone, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), trazodone, nefazodone, and venlafaxine, have demonstrated efficacy in management of anxiety disorders, several issues could limit their use[3-5]: intolerable adverse effects, patients' reluctance to take synthetic drugs, and patients' hesitation to seek prescriptions for anxiety.

Recent guidelines for treatment of anxiety disorders have placed antidepressants as first-line therapy, with benzodiazepines as second-line therapy.[6] Benzodiazepines might be useful as adjunctive therapy for patients just beginning antidepressant therapy. These factors could contribute to the increasing demand on family physicians to be aware of herbal products and their use in order to provide the best care for their patients.

Kava extract is a bitter herb from the *Piper methysticum* plant, a member of the black pepper family.[7] It has been used for centuries as a natural relaxant in the South Pacific. Its use was first documented by Captain James Cook, the western explorer, in 1768.[7] Kava's mechanism of action is unclear, but researchers think it preferentially involves the limbic structures (eg, hippocampus, amygdala) and exerts mild effects on γ-aminobutyric acid–A (GABA-A) binding sites. Kava might also alter central nervous system serotonin activity at 5-hydroxytryptamine$_{1A}$ receptors and exert an inhibitory effect on dopamine and norepinephrine.[7]

Kava extract was among the most frequently sold herbs in the United States in 1998.[7] It is considered effective therapy for anxiety in some European countries, such as Germany. But what evidence supports its use?

Overview of study and outcomes

This systematic review and meta-analysis involved an extensive literature search using MEDLINE, EMBASE, BIOSIS, AMED, CISCOM, and the Cochrane Library databases using the search terms kava, kawa, kavain, *Piper methysticum*, and Rauschpfeffer (German term for *Piper methysticum*). Bibliographies of studies and review articles on kava were manually searched, and experts and manufacturers of kava extract

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were contacted for further information. No language restrictions were applied to the searching strategies.

Only randomized, double-blind studies that used kava extract mono-preparations were included in the review. All articles were gathered by someone uninvolved in the study evaluation. Data were extracted and evaluated by two independent reviewers using standardized, defined criteria. All disagreements in data assessment were resolved by discussion between evaluators; consensus was reached in all cases. The scoring system devised by Jadad and associates[8] was used to assess the quality of each study.

Seven randomized, double-blind, placebo-controlled studies were included in the review. Three (N = 198) were analyzed in the meta-analysis. All three studies used the Hamilton Rating Scale for Anxiety (HAM-A)[9] to assess outcome. Patients enrolled in these studies had a baseline HAM-A score of 19 or greater. All trials used the same preparation of kava extract (WS1490) and the same dosing regimen of 100 mg by mouth three times daily (total kavapyrone dose was 210 mg/d). Slightly more than half (51%) the patients included in the meta-analysis were diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised (DSM-III-R) criteria for anxiety.

Results

All seven trials demonstrated significant reductions in anxiety among patients receiving kava extract. Numbers needed to treat (NNT) in the three studies included in the meta-analysis were six, 11, and 21. Therefore, treating six to 21 patients with kava extract for 4 to 24 weeks should mean a marked improvement in one patient's anxiety symptoms. Results of the meta-analysis demonstrate a significant reduction from baseline in HAM-A scores of the group receiving kava extract (weighted mean difference was 9.69; 95% confidence interval [CI] 3.54 to 15.83). Five of the seven trials reported adverse effects with kava extract, such as gastrointestinal complaints, restlessness, drowsiness, tremor, headache, and tiredness.

Analysis of methodology

All seven studies were randomized, double-blinded, and placebo-controlled, with a calculated mean quality score[8] of 4 out of 5 (median score: 5). All seven studies demonstrated a significant improvement in anxiety symptoms in patients who received kava extract rather than placebo. Some limitations apply to the methodology of these studies, however. All seven studies had small sample sizes, and most lacked a proper power calculation and were too short (4 weeks or less). In the four studies not included in the meta-analysis, differences existed with respect to type of kava preparation used, diagnostic criteria, and outcome measures. Three of the studies did not detail their randomization procedures.

Although the three studies included in the meta-analysis were homogeneous with respect to type of kava preparation, dosing regimen, and outcome measure, there were differences in the diagnostic criteria used. Only 51% of patients included in the meta-analysis were diagnosed using uniform diagnostic criteria (DSM-III-R). The largest and longest study included in the meta-analysis demonstrated a substantial placebo effect; the 95% CI approached 0 (weighted mean difference was ~5; 95% CI, ~1 to 9). The smallest study (N = 40) in the meta-analysis demonstrated the largest treatment effect (weighted mean difference was ~18; 95% CI 10 to 28), which would have positively influenced the meta-analysis result in favour of the efficacy of kava extract. Therefore, results of the meta-analysis could have been overstated due to this small trial. In addition, as with many studies pertaining to these preparations, a funnel plot to assess for publication bias was not performed.

Application to clinical practice

To apply the results of this meta-analysis to clinical practice, it is important to determine what types of patients were enrolled in the studies. Because almost all the studies included in this review were published in foreign journals, it is difficult to review patients' characteristics. More specifically, it is difficult to determine whether patients had other conditions, including other underlying psychiatric conditions; the severity of their symptoms; the types of anxiety disorders (eg, did all patients have generalized anxiety disorder?); and both the other antianxiety medications patients might have used in the past and their concurrent medications.

The controlled environment of a randomized trial might not apply to daily clinical practice because patients are often selected carefully according to defined criteria and are monitored closely. For example, it is typical to see patients with a single mental health condition in a trial, but it is often atypical in the community. Also, unregulated production of kava extract by various manufacturers could lead to inconsistencies in the efficacy and toxicity observed with this agent in practice. For example, it is difficult to determine whether all marketed preparations of kava extract produce similar efficacy to WS1490, the preparation used in the meta-analysis. In Canada, kava is available in various formulations (eg, powder, tincture, raw root), and the active constituent of kavapyrones can range anywhere from 4% to 55%. Some kava preparations (eg,

Kavatrol) contain a combination of several herbs, all of which should be evaluated separately for adverse effects and drug interactions.

Although, this review demonstrates that kava extract is more effective than placebo for treating patients with anxiety, the results should be interpreted with caution. As described above, the limitations of the available data make the results less convincing. More data are needed before kava extract can be recommended for use in clinical practice. Larger studies comparing kava extract to current standard treatment, such as SSRIs, are needed to firmly establish the role of kava in treatment of anxiety. Comparative trials are also needed to determine whether kava extract is better tolerated than conventional therapy.

Finally, family physicians and consumers need to be aware that kava extract can interact with other medications, such as psychopharmacologic agents (eg, benzodiazepines, TCAs, alcohol), which could lead to additive central nervous system effects and toxicity; anticoagulants (eg, warfarin), which could lead to additive antithrombotic activity; and antiparkinsonian agents (eg, levodopa), which could lead to antagonism of the medication effects.[7] Physicians should be extra cautious in using kava extract for patients taking many medications.

Bottom line

- This systematic review and meta-analysis of seven small randomized controlled trials demonstrated, to some extent, the safety and efficacy of kava extract for treatment of patients with anxiety disorders.
- Several limitations apply to the study's results, including small sample size, lack of power calculation in most trials, and lack of uniform diagnostic criteria.
- Kava might be pharmacologically similar to benzodiazepines, and, if it is, it might have short-term benefits that will not extend to the long-term efficacy of antidepressants or cognitive behavioural therapy.
- The lack of regulated, standardized preparations of kava extract contributes to potential inconsistencies in achieving outcomes similar to those in the controlled trials used in this meta-analysis.
- Comparative data with current antianxiety agents are needed to more clearly define the role of kava extract for patients with anxiety.
- Kava extract is not devoid of adverse effects and potential drug interactions.

Points saillants

- Cette revue systématique et méta-analyse de sept études aléatoires contrôlées de petite envergure ont démontré, dans une certaine mesure, l'innocuité et l'efficacité de l'extrait de kawa dans le traitement de patients souffrant de troubles anxieux.
- Les résultats de l'étude comportent plusieurs limitations, notamment la petite taille de l'échantillon, l'absence de calcul de l'efficacité statistique dans la plupart des études et le manque d'uniformité dans les critères diagnostiques.
- Le kawa pourrait être semblable sur le plan pharmacologique aux benzodiazépines et, si c'était le cas, il pourrait avoir des effets bénéfiques à court terme qui n'auraient pas l'efficacité à long terme des agents antidépressifs ou de la thérapie comportementale cognitive.
- L'absence de préparations réglementées et normalisées de l'extrait de kawa peut se traduire par d'éventuelles incohérences dans l'obtention de résultats semblables à ceux réalisés dans les études contrôlées sur lesquelles porte la méta-analyse.
- Il faudrait des données comparatives par rapport aux agents actuels contre les troubles anxieux pour définir plus précisément de rôle de l'extrait de kawa chez de tels patients.
- L'extrait de kawa n'est pas sans avoir d'effets indésirables et peut comporter des interactions médicamenteuses éventuelles.

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