A placebo-controlled study of Kava Kava in generalized anxiety disorder

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Kava in generalized anxiety disorder: three placebo-controlled trials

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In this study, we evaluated the efficacy and safety of kava kava (*Piper methysticum*) in generalized anxiety disorder. Data were analyzed from three randomized, double-blind, placebo-controlled trials of kava, including one study with an active comparator (venlafaxine), in adult outpatients with DSM-IV generalized anxiety disorder. The pooled sample ($n=64$) included the following number of participants: kava, $n=28$; placebo, $n=30$; and venlafaxine, $n=6$. Given the comparability of the study designs, the data comparing kava and placebo were then pooled for further efficacy and safety analyses. No significant differences were observed between the treatment groups in any of the trials. In the pooled analyses, no effects were found for kava, while a significant effect in favor of placebo was observed in participants with higher anxiety at baseline. No evidence of hepatotoxicity was found with kava, and all of the treatments were well tolerated. Findings from these three controlled trials do not support the use of kava in DSM-IV generalized anxiety disorder. *Int Clin*

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Introduction

The botanical treatment kava kava (*Piper methysticum*) has been used as a tranquilizing substance in Pacific Island cultures for thousands of years. More recently, it has been adopted in Western Europe for the treatment of anxiety and nervous tension. Pittler and Ernst (2003) have reviewed the available data, concluding that there is a strong effect of kava over placebo in anxiety. This review is based on comparatively few studies, in which diagnostic representation is very broad, with inclusion of a variety of clinical conditions, and no information as to the relative proportions of each disorder treated by kava or placebo. A second problem is the unusually high baseline Hamilton Anxiety (HAM-A) scores, which far exceed those typically found in US anxiety disorder trials.

With this information as the background, our group set about a series of trials that examined the effects of kava in randomized, double-blind, placebo-controlled studies of generalized anxiety disorder (GAD). Results of one trial have already been published (Connor and Davidson, 2002), while findings from the other two trials remain unpublished and are the subject of this report. Unfortunately, it was necessary to discontinue both trials prematurely because of concerns raised following reports of possible hepatotoxicity with kava (Russmann *et al.*, 2001).

We believe this is the largest sample in which kava has been evaluated in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition (April 1994)) GAD. While each study yielded only a small sample, our results are sufficiently interesting to warrant a clinical report. In aggregate, these studies represent a total of 58 patients treated with either kava or placebo and six with venlafaxine-XR, all of whom were treated in a broadly comparable fashion. Study 3 is the only trial, to our knowledge, that evaluates kava vs. a therapeutic dose of a standard pharmacotherapy and placebo in GAD. In this report, the studies are presented both individually and in a combined analysis. While acknowledging limitations in pooling these data, given the interest in and controversies surrounding kava and the broad appeal and use of complementary and alternative modalities in general, and especially for chronic conditions such as anxiety (Eisenberg *et al.*, 1998), we think it of value to report our findings.

Materials and methods

Study sample

The study sample comprised data from three controlled trials of kava in GAD. The first trial (Connor and Davidson, 2002) was a 4-week evaluation of kava vs placebo in patients who fulfilled DSM-IV criteria for GAD, using a modified duration requirement of 1 month,

and with a minimum baseline HAM-A Scale (Hamilton, 1959) score of 16. A second trial was conducted using similar entry criteria, including patients with milder anxiety symptoms (baseline HAM-A score of 12–20). The third study was a randomized trial of patients meeting DSM-IV criteria for GAD (including minimum symptom duration of 6 months) of moderate severity (minimum baseline HAM-A score of 18) who were randomized to 8 weeks of treatment with kava, venlafaxine-XR, or placebo. In each study, double-blind treatment was preceded by a 1-week, single-blind placebo run-in period. Patients who failed to meet the entry criteria following the run-in period were excluded from the study.

Key exclusion criteria included the following: history within the previous 6 months of major depression, panic disorder, obsessive–compulsive disorder, or posttraumatic stress disorder; history within previous 12 months of a substance use disorder (6 months for study 3); a lifetime history of bipolar disorder, psychotic disorder, organic brain syndrome, or mental retardation; clinically significant abnormalities on screening laboratory tests or electrocardiograms; an unstable medical condition; prescription medications or medicinal herbs with psychotropic effects; or pregnancy or lactation.

Each study was approved by the Duke University Medical Center Institutional Review Board. All patients provided written informed consent before completing any study procedures. Study and baseline sample characteristics for each trial are presented in Table 1.

Study medication used in the first two trials was provided by Pure World Botanicals Inc. (Hackensack, New Jersey, USA). Kava and matching placebo for the third study were provided by Dr Willmar Schwabe GmbH & Co (Germany) and corresponded to the formulation used in European studies funded by this company. In each case, kava was administered in an oral capsule. Kavapyrones, or kavalactones, are considered the active constituent of the herb, and each capsule was standardized to 70 mg kavalactones. The dose of kava (KAV) in each trial was initiated at 140 mg kavalactones per day (70 mg kavalactones twice daily) for 1 week and then increased to 280 mg kavalactones per day (140 mg kavalactones twice daily). In the third trial, a double-dummy design was employed, with placebo (PBO) matched for kava and for venlafaxine-XR (VEN), with the dose of venlafaxine-XR started at 37.5 mg/day and titrated to a maximum daily dose of 225 mg.

Clinical assessments were virtually identical in the three studies and included the HAM-A Scale (Hamilton, 1959), the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), and the Sheehan Disability Inventory (SDI) (Sheehan, 1983). Safety assessments conducted in each trial included liver function tests, which were performed at screening and at the completion of treatment. As a result of recent concerns regarding the potential hepatotoxic effects of kava, these data are also presented in this report.

Statistical analyses

Analyses were performed on the intention-to-treat group, which included all patients who received at least one dose of double-blind study medication and returned for at least one post-randomization efficacy evaluation. Results are provided for the individual studies and for the pooled sample of patients treated with kava or placebo.

Of chief interest was the overall efficacy of kava vs placebo and, to the extent possible, vs. venlafaxine-XR. Continuous measures were assessed using either the Wilcoxon rank sum test (for data from the individual studies, which were non-normally distributed) or analysis of variance, with treatment and study included in the model (for pooled data). Rates of response (reduction of $> 50\%$ in HAM-A score from baseline) and remission (HAM-A score of < 7 at endpoint) were also assessed in each study and in the pooled kava–placebo sample using a χ^2 test. All tests were two-tailed and were performed at a significance level of $\alpha = 0.05$.

It has been reported previously that the baseline anxiety level influences the outcome in GAD patients treated with kava, whereby kava works more effectively in milder

Table 1 Study and baseline sample characteristics of participants in three controlled trials of kava in GAD ($n=64$)

Study	Patients (n)	Entry criteria	Treatment groups (n), maximum dosage	Treatment duration (weeks)	Sex (% female)	Ethnicity (% white)	Age, years (mean SD)
1	35	DSM-IV GAD[a], baseline HAM-A ≥ 16	Kava ($n=17$), 280 mg kl/day, placebo ($n=18$)	4	80	97	52.5 (11.4)
2	13	DSM-IV GAD[a], baseline HAM-A: 12–20	Kava ($n=6$), 280 mg kl/day, placebo ($n=7$)	4	69	92	49.9 (14.9)
3	16	DSM-IV GAD, baseline HAM-A ≥ 18	Kava ($n=5$), 280 mg kl/day, venlafaxine-XR ($n=6$), 225 mg/day, placebo ($n=5$)	8	56	88	43.6 (11.1)

GAD, generalized anxiety disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-4th edition.; HAM-A, Hamilton Anxiety Scale; kl, kavalactone.
[a]Minimum symptom duration of 1 month.

forms of GAD (Connor and Davidson, 2002). To test this finding in a larger sample, data for all patients treated with kava or placebo were pooled and the sample was then divided by median pretreatment HAM-A score into high (HAM-A > 19) and low (HAM-A < 19) anxiety groups. The treatment conditions were compared using analysis of covariance, using a regressed change score model (Cohen and Cohen, 1975). Significant effects were followed by analysis of the differences between means using Tukey contrasts (using the error term from the analysis of covariance model) to compare the kava and placebo treatment groups.

The effect of kava and placebo on liver function was evaluated in the pooled sample. Alterations in liver function were assessed by treatment group, comparing changes in liver enzymes (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin) over the course of treatment using the Wilcoxon signed rank test.

Results

Demographic data for the three studies are presented in Table 1. The pooled sample ($n = 64$) was predominantly female (72%) and Caucasian (94%), with a mean age of 50 years. Symptom severity before and after treatment on the three outcome measures (HAM-A, HADS-A, and SDI) by treatment are presented by study and for the pooled sample in Table 2.

Individual studies

Patients had symptoms consistent with GAD of moderate severity. In study 1, a significant effect was observed in favor of PBO on the SDI (Kruskal–Wallis $\chi^2 = 4.85$, d.f. 1, $P < 0.03$). In study 2, a trend was found in favor of KAV on the HAM-A (Kruskal–Wallis $\chi^2 = 3.78$, d.f. 1, $P = 0.05$). No other differences were observed between the treatment groups on any of the other continuous outcome measures or in the rates of treatment response, which were as follows: KAV, 0–50%; PBO, 29–60%; and VEN, 50%. Further, no treatment differences were noted in terms of remission rates, which were as follows: study 1, KAV 24% ($n = 4$), PBO 22% ($n = 4$); study 2, KAV 50% ($n = 3$), PBO 29% ($n = 2$); and study 3, KAV 0% ($n = 0$), PBO 0% ($n = 0$), and VEN 33% ($n = 2$).

Pooled sample

Significant effects in favor of PBO were found on the HAM-A ($F = 4.45$, d.f. 1, $P < 0.04$) and the HADS ($F = 4.15$, d.f. 1, $P < 0.05$). A significant effect was also observed for study on the HAM-A ($F = 15.96$, d.f. 2, $P < 0.0001$), and this can be explained by lower HAM-A entry criterion in study 2. Lastly, we found a significant study by treatment interaction on the SDI ($F = 3.54$, d.f. 2, $P < 0.04$), with a trend toward significance on the HADS ($F = 2.78$, d.f. 2, $P < 0.07$). When the groups were compared by baseline anxiety level, a significant treatment by baseline anxiety level interaction was found on both the HADS and the SDI Scales (Table 3). Tukey's tests between means showed an effect in favor of placebo in high anxiety on both the HADS and the SDI Scales. Remission rates in the pooled samples were as follows: KAV, 25% ($n = 7$); PBO 20% ($n = 6$); and VEN 33% ($n = 2$) (NS).

Effect of kava on liver function

Assessment of changes in hepatic enzymes showed no evidence that either kava or placebo was associated with significant alteration in liver function (Table 4). Slightly

Table 3 Mean change from baseline on the HADS and SDI at endpoint by baseline anxiety level

	Kava		Placebo		
	n	Mean (SD)	*n*	Mean (SD)	*P*
HADS[a]					
Low anxiety	11	−4.9 (6.0)	19	−2.0 (3.8)	NS
High anxiety	15	0.8 (3.9)	12	−2.9 (4.2)	<0.05
SDI[b]					
Low anxiety	11	−4.6 (3.7)	19	−2.2 (5.1)	NS
High anxiety	15	0.1 (3.7)	12	−6.2 (4.5)	<0.001

HADS, Hospital Anxiety and Depression Scale; SDI, Sheehan Disability Inventory; low anxiety: baseline HAM-A ≤ 19; high anxiety: baseline HAM-A > 19.
[a]Tukey's test: F = 7.70, d.f. 1, 53, $P < 0.01$.
[b]Tukey's test: F = 13.20, d.f. 1, 53, $P < 0.001$.

Table 2 Symptom severity on outcome measures before and after treatment by study and treatment group (median Q1, Q3)

	Study 1		Study 2		Study 3			Pooled data	
	KAV	PBO	KAV	PBO	KAV	PBO	VEN	KAV	PBO
HAM-A	*n* = 17	*n* = 18	*n* = 6	*n* = 7	*n* = 5	*n* = 5	*n* = 6	*n* = 28	*n* = 30
Before	21 (18, 21)	18 (16, 21)	17 (16, 18)	14 (13, 20)	32 (24, 34)	24 (20, 28)	29 (28, 32)	20.5 (18, 22)	18 (16, 21)
After	13 (9, 21)	10 (8, 13)	7.5 (3, 12)	10 (4, 17)	20 (20, 26)	12 (10, 20)	16 (6, 22)	13.5 (8, 20.5)	10 (8, 14)
HADS	*n* = 17	*n* = 18	*n* = 6	*n* = 7	*n* = 5	*n* = 5	*n* = 6	*n* = 27	*n* = 30
Before	17 (12, 19)	16 (12, 20)	18 (14, 19)	15 (14, 20)	21 (18, 23)	14 (11, 16)	17.5 (16, 19)	17 (14, 21)	16 (12, 17)
After	17 (12, 20)	13.5 (9, 17)	10.5 (9, 15)	14 (12, 16)	18 (14, 18)	12 (11, 17)	14 (13, 15)	15.5 (10, 18.5)	13.5 (11, 17)
SDI	*n* = 17	*n* = 18	*n* = 6	*n* = 7	*n* = 5	*n* = 5	*n* = 5	*n* = 27	*n* = 30
Before	10 (5, 13)	12 (9, 17)	5 (0, 12)	14 (5, 15)	8 (7, 18)	1 (1, 10)	10 (0, 12)	9 (5, 13)	12 (6, 16)
After	10 (4, 12)	8.5(4, 13)	2 (0, 4)	7 (3, 15)	6 (3, 14)	2 (2, 2)	6 (2, 12)	5 (1, 12)	7 (2, 13)
Response rate[a]	*n* = 6, 35%	*n* = 9, 50%	*n* = 3, 50%	*n* = 2, 29%	*n* = 0, 0%	*n* = 3, 60%	*n* = 3, 50%	*n* = 9, 32%	*n* = 14, 47%

HAM-A, Hamilton Anxiety Scale; HADS, Hospital Anxiety and Depression Scale; SDI, Sheehan Disability Inventory; KAV, kava; PBO, placebo.
[a]Response: ≥ 50% reduction in HAM-A score from baseline.

Table 4 Liver enzyme scores by treatment group (mean SD)

	Treatment		
	Before	After	P
SGOT			
Kava	25.9 (6.8)	30.0 (14.5)	NS
Placebo	26.8 (9.5)	24.6 (5.0)	
SGPT			
Kava	27.9 (13.8)	34.3 (24.7)	NS
Placebo	28.0 (12.6)	26.7 (9.1)	
Alkaline phosphatase			
Kava	67.9 (16.9)	69.6 (14.4)	NS
Placebo	67.6 (12.0)	63.2 (19.8)	
Total bilirubin			
Kava	0.55 (0.23)	0.50 (0.24)	NS
Placebo	0.49 (0.20)	0.48 (0.18)	

Reference ranges: serum glutamate-oxaloacetate transaminase (SGOT), 10–60 U/l; serum glutamate-pyruvate transaminase (SGPT), 10–60 U/l; alkaline phosphatase, 30–135 U/l; total bilirubin, 0.2–1.2 mg/dl.

elevated alanine aminotransferase values were observed in three patients on kava, but these changes were determined to be not clinically significant, as noted in a previous report (Connor *et al.*, 2001).

Discussion

Use of kava in these study populations failed to confirm any beneficial effect in GAD. While this botanical treatment was well tolerated (Connor *et al.*, 2001) and appeared safe in this limited sample with respect to liver function, its therapeutic benefit was not readily apparent. While the treatments did not differ significantly with respect to rates of remission, one quarter of patients treated with kava met the criteria for remission. In contrast, venlafaxine-XR produced a 33% remission rate in study 3, which is in line with results from the larger pool of data obtained in the pivotal GAD trials (Montgomery *et al.*, 2002).

While there was a numerical difference in response rates in favor of kava in study 2, the small sample size precludes this finding from showing any degree of statistical significance. Further, in contrast to findings from a previous report (Connor and Davidson, 2002), the baseline anxiety level did not influence response to kava, although those with more severe anxiety appeared more responsive to placebo, a paradoxical finding. These results highlight several important points. First, the placebo responsivity of GAD is a challenge to investigating this disorder using a currently accepted study methodology. Further, we were surprised to find a stronger placebo effect with the more severe form of GAD. Second, we observed that patients participating in these studies were highly motivated for kava to demonstrate an effect in GAD, with strong beliefs in the beneficial effect of botanical treatments, and it is very likely that these beliefs might have influenced their response to treatment and contributed to the lack of an observable treatment difference. Lastly, the samples from which the data were drawn were not large, considerably smaller than the placebo-controlled trials in which kava has demonstrated benefit in GAD ($n = 101$, Volz and Kieser, 1997; $n = 58$, Kinzler *et al.*, 1991), and it is possible that the pooled sample lacked adequate statistical power to detect a treatment difference. Further, given the large numerical differences in favor of placebo, one also needs to consider the possibility of a type II error.

Following case reports of hepatitis in kava users in 2001 and 2002, concern was raised about the potential hepatotoxicity of kava, as a botanical product available over the counter and widely used in Europe. While no changes in liver function were found in our studies, which used comparatively high doses of kavapyrones, the issue of liver toxicity is a potentially serious concern. No consistent pattern of toxicity has emerged and, in general, the disparity in toxicity patterns observed could arise from genetic differences in human metabolism (Russmann *et al.*, 2001), differences in kavapyrone extraction processes (Currie and Clough, 2003; Whitton *et al.*, 2003), and differences in kava raw materials used (Dragull *et al.*, 2003; Nerurkar *et al.*, 2004). Three possible mechanisms for kavapyrone-associated hepatotoxicity are known: inhibition of cytochrome P450 enzymes, reduction in liver glutathione content, and, more remotely, inhibition of cyclooxygenase enzyme activity (Clouatre, 2004). While still not fully understood, recent work (Mathews *et al.*, 2002) has demonstrated very substantial inhibition of the cytochrome isoenzymes 1A2, 2C9, 2C19, 2D6, and 3A4, such that it is likely that when co-administered with a variety of other medications, including common analgesics, kava could trigger serious hepatotoxicity. Newer formulations, free from methysticin and dihydromethysticin may result in a safer form of kava with a wider potential.

We acknowledge several limitations in this study that should be considered in interpreting the report's findings. Firstly, it is important to consider the limitations inherent in using and interpreting findings from analyses of pooled data. Secondly, the samples from which the data were drawn were relatively small, particularly the venlafaxine-XR sample. Thirdly, while the study designs of the studies included in this report were very similar, there were several differences, most notably in the duration of GAD at study entry (1 month for studies 1 and 2 vs 6 months for study 3) and in the duration of study treatment (4 weeks for studies 1 and 2 vs 8 weeks for study 3). Lastly, the average age of patients (50 years) is considerably higher than the average age of participants in controlled treatment trials of GAD, here subjects tend to be in the mid to late 30s, and this difference could influence the generalizability of the study results.

In summary, our results suggest that kava is ineffective in GAD as diagnosed by DSM-IV criteria. This is contrary to the findings from a recent multicenter trial of 129

patients with GAD that compared kava with two active comparators, the 5-hydroxytryptamine-1a partial agonist buspirone and the tricyclic and nonselective σ site ligand opipramol, and found no differences between the groups after 8 weeks of treatment (Boerner *et al.*, 2003). While the authors concluded that kava was as effective as the other drugs in treating GAD, the doses of buspirone (10 mg) and opipramol (100 mg) used in the trial would be considered by many to be subtherapeutic, given the therapeutic dosing ranges of 15–60 mg/day for buspirone and up to 200 mg/day for opipramol in GAD (Moller *et al.*, 2001). This dosing regimen thus calls into question the clinical significance of the results reported in the Boerner *et al.* trial. Moreover, the lack of a placebo arm further limits the conclusions that can be drawn from this report. Nonetheless, it is indeed possible that milder stress reactions could respond to kava (Cropley *et al.*, 2002) and, along with possible increases (i.e. improvement) in heart rate variability with kava in anxiety (Watkins *et al.*, 2001), these certainly remain appealing aspects of the plant. Under such circumstances of treating mild stress reactions, however, one must carefully make a risk–benefit assessment of treating with kava, where it appears that the risks exceed the potential benefit. Thus, at the present time, it is hard to justify recommending kava's use in clinical psychiatry.

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