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

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We assessed the efficacy and safety of a botanical anxiolytic, Kava kava (*Piper methysticum*), in treating generalized anxiety disorder (GAD). Thirty-seven adults with DSM-IV GAD were randomly assigned to 4 weeks of double-blind treatment with kava or a matching placebo. Weekly efficacy assessments [Hamilton Anxiety Scale, Hospital Anxiety and Depression Scale (HADS), Self Assessment of Resilience and Anxiety (SARA)] and safety evaluations were conducted. Improvement was observed with both treatments but no differences were found in the principal analysis. Post-hoc analyses revealed significant differences based on baseline anxiety severity, whereby kava was superior on the SARA in low anxiety and placebo was superior on the HADS and SARA in high anxiety. Both treatments were well tolerated. Although kava was not superior to placebo, it would be premature to rule it out as efficacious in GAD. Int Clin Psychopharmacol 17:185–188 © 2002 Lippincott Williams & Wilkins

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INTRODUCTION

Interest in medicinal herbs has grown dramatically in the last decade, including the application of these treatments to anxiety. One phytomedicine widely reported to have anxiolytic effects is Kava kava (*Piper methysticum*). Used for centuries as a calmative in the South Pacific Islands, kava has demonstrated anxiolytic activity in animal models, with evidence suggesting activity mediated by GABAergic, serotonergic, noradrenergic and dopaminergic mechanisms (Jossofie *et al*., 1994; Seitz *et al*., 1997; Baum *et al*., 1998). In controlled clinical studies of various anxiety states, kava has demonstrated superior efficacy to placebo (Pittler and Ernst, 2000) and equal to benzodiazepines, but with fewer side-effects (Woelk *et al*., 1993). However, these studies examined heterogeneous anxiety states and therefore call into question how the results might be applied clinically. With these considerations in mind, we undertook the first randomized, double-blind, placebo-controlled trial of kava in adults meeting DSM-IV criteria for generalized anxiety disorder (GAD).

METHODS

Adult outpatients were screened for the presence of GAD, modified to a duration of at least 1 month, using the MINI structured interview (Sheehan *et al*., 1998) and a clinical interview. The decision to use a 1-month duration criterion was based on the recognition that many people are likely to turn to kava for relief of more brief stress-related episodes. Furthermore, there is evidence in women that GAD of 1 month duration does not differ in genetic contribution from a GAD of 6 months duration (Kendler *et al*., 1992). Subjects meeting the following criteria were excluded: Hamilton Anxiety Scale (HAM-A; Hamilton, 1959) score of <16 at screen and baseline; within the previous 6 months, a history of or treatment for major depression, panic disorder, obsessive–compulsive disorder or post-traumatic stress disorder; lifetime history of psychosis, organic brain syndrome or mental retardation; history of substance abuse within the last 12 months; concurrent use of psychotropic medications or medicinal herbs; clinically meaningful abnormalities on screening laboratory tests or electrocardiogram (ECG); and an

unstable medical condition. Following a 1-week placebo lead-in, subjects who continued to meet entry criteria were randomly assigned, using a computer-generated randomization, to double-blind treatment with either kava (KavaPure®; KAV), standardized to 70 mg kavalactones (kl), or matching placebo (PBO). Treatment was initiated at 70 mg kl b.i.d. for 1 week (140 mg kl/day) and increased to 140 mg kl b.i.d. (280 mg kl/day) for the next 3 weeks.

Subjects were evaluated weekly for treatment efficacy with the following assessments: HAM-A; Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983); and Self-Assessment of Resilience and Anxiety (SARA; Barnett *et al*., 2001). The SARA was developed specifically with the effects of kava in mind, and with the hope that it would be helpful in assessing milder, subclinical anxiety states (e.g. those present in non-treatment seeking samples who may seek relief through alternative therapies or over the counter treatments, including medicinal herbs). The eight-item SARA assesses the following features: feeling relaxed, calm, confident, free of worries and sociable; focused thoughts; not avoiding things because of fear; and bouncing back after stress. Each item is rated from 0 (not at all) to 10 (extremely), with higher scores reflecting greater resilience or less anxiety. Psychometric properties of the scale have been published elsewhere (Barnett *et al*. 2001).

Safety was monitored by evaluation of vital signs, laboratory and ECG assessments pre- and post-treatment, medication side-effects and withdrawal symptoms, and details of these have been published previously (Connor *et al*., 2001). The protocol received institutional review board approval and, after receiving a complete description of the study, subjects gave their written informed consent.

Primary efficacy measures included the HAM-A and HADS. Parametric statistical tests were used to analyse the HADS and SARA scores and nonparametric tests for HAM-A scores, given that the HAM-A baseline scores were non-normally distributed. Between treatment comparisons were made using either Student's *t* or Kruskal–Wallis tests.

A post-hoc analysis compared KAV to PBO by severity of baseline anxiety. Based on a median pretreatment HAM-A score of 18, a score which reflects moderate clinical anxiety, the sample was divided into High (HAM-A >18) and Low (HAM-A ≤ 18) anxiety groups. The treatments were compared in a 2×2 ANCOVA using a regressed change score model (Cohen and Cohen, 1975). Significant effects were followed by analysis of the differences between means with Tukey contrasts (using the error term from the ANCOVA model) to compare the KAV to PBO conditions.

RESULTS

Thirty-eight subjects were randomized, including 31 female (82%) and 32 Caucasian participants (97%), with a mean (SD) age of 51.7 (11.6) years (range 31–75 years). Three subjects withdrew their consent following the baseline visit (work schedule conflict; development of acne; nausea) and did not return for further assessment, leaving 35 subjects in the evaluable sample. Improvement was noted in both groups, with response rates (i.e. $\geq 50\%$ reduction in baseline HAM-A scores) of 35% ($n=6$) and 50% ($n=9$) in the KAV and PBO groups, respectively. However, no statistically significant differences were observed between the groups on any of the efficacy assessments (Table 1).

Post-hoc analyses showed a significant interaction of treatment by baseline anxiety for the HADS and SARA scales (Table 2). Tukey's tests between means on the HADS showed greater improvement for PBO in the high anxiety group, but no difference in the low anxiety group. Analysis of the SARA showed greater improvement for KAV compared to PBO in the low

Table 1. Mean baseline and endpoint scores on outcome measures in generalized anxiety disorder

	Kava		Placebo		Test value	d.f.	*P*
	n	Mean ± SD	*n*	Mean ± SD			
HAM-A							
Baseline	19	19.9 ± 4.1	18	18.8 ± 2.9	$\chi^2 = 2.56$	1	NS
End	17	14.2 ± 8.3	18	10.3 ± 4.4	$\chi^2 = 2.02$	1	NS
HADS							
Baseline	19	16.2 ± 4.1	18	15.7 ± 4.0	$t = 0.41$	35	NS
End	17	15.9 ± 5.5	18	13.2 ± 4.7	$t = 1.57$	33	NS
SARA							
Baseline	19	32.9 ± 13.0	18	34.4 ± 8.9	$t = -0.41$	35	NS
End	17	38.9 ± 14.8	18	41.4 ± 14.1	$t = -0.51$	33	NS

HAM-A, Hamilton Anxiety Scale; HADS, Hospital Anxiety and Depression Scale; NS, not significant.

Table 2. Mean baseline and endpoint scores on HADS and SARA by baseline anxiety level

	Kava		Placebo		*P*
	n	Mean ± SD	*n*	Mean ± SD	
HADS*					
Low anxiety					
Baseline	6	17.5 ± 3.3	11	14.5 ± 2.8	NS
End	6	13.7 ± 5.5	11	12.9 ± 3.7	
High anxiety					
Baseline	11	16.1 ± 4.4	7	17.6 ± 5.0	< 0.05
End	11	17.2 ± 5.4	7	13.7 ± 6.4	
SARA†					
Low anxiety					
Baseline	6	29.8 ± 11.0	11	36.0 ± 8.7	< 0.01
End	6	45.7 ± 13.6	11	39.8 ± 13.3	
High anxiety					
Baseline	11	32.1 ± 13.9	7	31.9 ± 9.2	< 0.05
End	11	35.2 ± 14.8	7	43.9 ± 16.0	

HADS, Hospital Anxiety and Depression Scale; SARA, Self Assessment of Resilience and Anxiety; NS, not significant. Low anxiety: baseline HAM-A ≤18; High anxiety: baseline HAM-A > 18. *Tukey's test: $F = 4.82$, d.f. =1, 30, $P < 0.05$. †Tukey's test: $F = 7.72$, d.f. =1, 30, $P < 0.01$.

anxiety group, but the KAV-PBO difference was in the opposite direction for the high anxiety group.

The treatments were well-tolerated and there was no evidence of withdrawal or sexual side-effects. Further details of the safety evaluation have been reported previously (Connor *et al*., 2001).

DISCUSSION

It is possible that negative study results for kava may exist, and which remain unpublished, yet dissemination of negative trials is scientifically important. In this study of patients with GAD of mild to moderate severity, kava was no different from placebo. These findings are in contrast to those obtained in other studies and may be attributable to several factors, such as the high placebo response rate observed and the uniqueness of the sample (e.g. seeking an alternative treatment modality with medicinal herbs; increased age relative to other studies of GAD; predominance of Caucasian females; milder level of baseline anxiety). Some may consider the treatment period insufficient, but if no benefit has been forthcoming after 4 weeks, it is unlikely that a treatment for GAD would be particularly appealing, since most effective treatments are significantly better than placebo by 1 or 2 weeks.

Nonetheless, a post-hoc analysis suggested that kava was significantly better than placebo in milder anxiety, with over a 50% reduction in the SARA score for subjects receiving kava compared to 11% on placebo. While placebo was superior in high anxiety, we are unable to explain unable to explain this finding.

Recently, concerns have been raised about the safety of kava following 28 cases of hepatosis, including several cases of hepatic failure requiring liver transplantation. While a causal relationship between kava and the liver abnormalities has not been clearly established, this is an area of active investigation at this time. In the present study, kava treatment was associated with good tolerance. Three subjects receiving kava experienced slight elevations in alanine aminotransferasase (one of whom had a borderline elevation at baseline), but this were not felt to be clinically significant. Kava did not demonstrate any sexual withdrawal symptoms upon discontinuation.

In summary, despite negative findings in the principal analysis, the results from the post-hoc analyses suggest that kava could be effective in mild GAD. These results should be interpreted with caution, however, given the pilot nature of the study, the relatively small sample size and the post-hoc aspect of the analysis. It is conceivable that our findings represent a type II error; therefore, we would consider it premature to rule out kava as a therapeutically useful agent in anxiety. We suggest that further studies be conducted, assuming that adequate safety can be established for kava.

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