Kava in the Treatment of Generalized Anxiety Disorder A Double-Blind, Randomized, Placebo-Controlled Study

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Kava in the Treatment of Generalized Anxiety Disorder
A Double-Blind, Randomized, Placebo-Controlled Study

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Abstract: Kava (Piper methysticum) is a plant-based medicine, which has been previously shown to reduce anxiety. To date, however, no placebo-controlled trial assessing kava in the treatment of generalized anxiety disorder (GAD) has been completed. A total of 75 participants with GAD and no comorbid mood disorder were enrolled in a 6-week double-blind trial of an aqueous extract of kava (120/240 mg of kavalactones per day depending on response) versus placebo. γ-Aminobutyric acid (GABA) and noradrenaline transporter polymorphisms were also analyzed as potential pharmacogenetic markers of response. Reduction in anxiety was measured using the Hamilton Anxiety Rating Scale (HAMA) as the primary outcome. Intention-to-treat analysis was performed on 58 participants who met inclusion criteria after an initial 1 week placebo run-in phase. Results revealed a significant reduction in anxiety for the kava group compared with the placebo group with a moderate effect size (P = 0.046, Cohen d = 0.62). Among participants with mild to severe Diagnostic and Statistical Manual of Mental Disorders–diagnosed GAD, this effect was larger (P = 0.02; d = 0.82). At conclusion of the controlled phase, 26% of the kava group were classified as remitted (HAMA ≤ 7) compared with 6% of the placebo group (P = 0.04). Within the kava group, GABA transporter polymorphisms rs2601126 (P = 0.021) and rs2697153 (P = 0.046) were associated with HAMA reduction. Kava was well tolerated, and aside from more headaches reported in the kava group (P = 0.05), no other significant differences between groups occurred for any other adverse effects, nor for liver function tests. Standardized kava may be a moderately effective short-term option for the treatment of GAD. Furthermore, specific GABA transporter polymorphisms appear to potentially modify anxiolytic response to kava.

Key Words: generalized anxiety disorder, anxiety, kava, Piper methysticum, pharmacogenetics, polymorphisms, GABA transporters, KALM project

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Generalized anxiety disorder (GAD) is a disabling condition that presents with a chronic course. Present pharmacotherapies used to treat GAD, whereas efficacious, have a modest clinical effect, as evidenced by a 2007 meta-analysis showing effect sizes of 0.36, 0.38, 0.50, and 0.45 for benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), pregabalin, and hydroxyzine, respectively. Because of this, more treatment options are required.

Plant-based medicines may provide a potential pharmacotherapeutic option, as evidenced by a recent positive double-blind, randomized controlled study (RCT) using chamomile for GAD (see Amsterdam et al1). Another such potential option is kava (Piper methysticum). Kava is a South Pacific plant medicine with traditional cultural use as an inebriant and modern clinical use as an anxiolytic. Numerous in vivo and in vitro models suggest several mechanisms by which kava may mediate a broad spectrum of psychopharmacologic actions from its psychoactive constituents, known as kavalactones. These actions include blockade of voltage-gated sodium ion channels, reduced excitatory neurotransmitter release from blockade of calcium ion channels, enhanced ligand binding to γ-aminobutyric acid (GABA) type A receptors, reversible inhibition of monoamine oxidase B, inhibition of cyclooxygenase, and reduced neuronal reuptake of dopamine and noradrenaline. A Cochrane review and meta-analysis of 6 RCTs using kava monopreparations (60–280 mg of kavalactones) for the treatment of anxiety found a significant reduction of anxiety on the Hamilton Anxiety Rating Scale (HAMA) for those receiving kava compared with placebo (weighted mean difference, 5.0; 95% confidence interval, 1.1–8.8; P = 0.01). Our pooled analysis of 6 studies using kava versus placebo in the treatment of generalized anxiety also found a significant effect in favor of kava on HAMA, with a Cohen d of 1.1.

Our previous work has revealed that a standardized water-soluble extract of kava (containing a total of 250 mg of kavalactones per day) is effective for the treatment of chronic generalized anxiety. The Kava Anxiety Depression Spectrum Study was a 3-week placebo-controlled, double-blind, crossover trial that recruited 60 adult participants with 1 month or more of elevated generalized anxiety. The results revealed that short-term administration of kava significantly reduced participants’ anxiety on the HAMA with a large effect size (d = 2.24). Our aim was to build on this work in a sample of adults with a tightly defined clinical diagnosis of GAD and no comorbid depression. This is of interest, as apart from a pooled analysis by Connor et al16 in 2006 of 3 incomplete kava GAD studies in which recruitment did not reach the required sample target (because of concerns over potential kava hepatotoxicity), no similar RCTs have been completed.

In addition, the genetic polymorphisms of 2 key neurobiological pathways were assessed in our study. GABAergic and...
noradrenergic pathways have been shown in preclinical models as the key mechanisms of kava’s psychotropic action. Our recent research has revealed that noradrenaline transporter (SLC6A2) rs3785157-T allele and rs2242446-T allele carriers were associated with a differing response to kava. We thereby aimed to explore the impact of genetic polymorphisms in the SLC6A2 and SLC 6A1 genes, which code for the noradrenalin and GABA transporter proteins, respectively. Neurochemical polymorphisms (ie, serotonin transporters) have been found to modify patient’s response to SSRIs; however, pharmacogenetics for kava remain presently unknown. Determining which select polymorphisms may modify response to kava may allow for a more judicious clinical application.

Rigorous controlled studies using standardized pharmacologic-grade kava are vital to assess if this is a valid pharmacologic approach to treating GAD. Thus, this RCT was performed to study the efficacy and safety of kava in GAD, whereas a further innovative aim was to explore potential key pharmacodynamic genetic correlates that may affect kava response.

**MATERIALS AND METHODS**

**Study Design**

The study was a controlled, double-blind trial involving the chronic administration of kava or placebo over 6 weeks (in addition to a 1-week placebo run-in phase, and a 1-week single-blind poststudy observation phase). Adult participants with Diagnostic and Statistical Manual of Mental Disorders (DSM–IV)–diagnosed GAD were recruited between March and December 2011 at a university research institution in Melbourne, Victoria, Australia. To maintain experimenter blinding, group allocation was performed by an independent third party who did not take further part in the study. Allocation to treatment groups was performed via computer, randomly assigning every participant to a group according to a Latin squares design. Both the researcher and participants were blinded as to which intervention was being administered, with the tablets being presented to the participants in an opaque sealed envelope. The study was approved by the Swinburne University Human Research Ethics Committee (ethics number 0254). The trial was registered on The Australian and New Zealand Clinical Trials Register (no. 12610000381088).

**Participants**

Adults (male and female) between 18 and 65 years old with DSM-IV–diagnosed GAD were recruited. To provide a tightly defined GAD phenotype, participants with major depressive disorder (MDD) or elevated depressive symptomatology (>17 on Montgomery-Asberg Depression Ratings Scale or MADRS) were excluded. Exclusion criteria included the following: (a) DSM-IV diagnosis of a psychotic or bipolar disorder illness, or MDD; (b) significant suicidal ideation in the previous 6 months; (c) current use of a range of medications, for example, antidepressants, mood stabilizers, antipsychotics, opioid analgesics, St John’s wort (a 4-week washout was permitted); (d) diagnosed hepatobiliary disease/inflammation; (e) substance abuse or dependency disorder in the previous 6 months, including alcohol; (f) previous adverse reaction to kava or benzodiazepines; (g) regular use of kava or benzodiazepines in the previous 12 months; (h) more than 1 occasion of benzodiazepine or kava use each week over the past month; (i) pregnancy or women trying to conceive, or those not practicing adequate contraception; (j) lack of facility in written or spoken English; and (k) abnormal baseline liver function.

**Interventions**

Tablets were formulated from a pressed, dried aqueous kava (peeled rootstock) extract standardized to contain 60 mg of kavalactones per tablet for a total daily dose of 120 mg of kavalactones (one 3-g tablet twice per day) for the first 3-week controlled phase, being titrated to 240 mg of kavalactones in nonresponse at the 3-week mark for the second 3-week controlled phase (two 3-g tablets twice per day). Kava placebo tablets were designed to be identical in appearance to the active intervention. Placebo tablets were formulated using a color-film coat identical in appearance to the herbal tablets. The excipients in the placebo tablets were calcium hydrogen phosphate, micro-crystalline cellulose, sodium starch glycollate, and magnesium stearate. The kava tablets were supplied by Integra Healthcare (Brisbane, Queensland, Australia) and manufactured under strict pharmaceutical good manufacturing practice. An independent assay of the kava tablets using high-performance liquid chromatography was conducted by Southern Cross University: Southern Cross Plant Science (Lismore, Australia). The analysis of the kavalactones revealed the following: dihydromethysticin (15.5 mg, 26%), kavain (12.5 mg, 21%), dihydromethysticin (11 mg, 18%), methysticin (8.5 mg, 14%), yangonin (8 mg, 13%), desmethoxyyangonin (5 mg, 8%), whereas the alkaloid pipermethystine was not present.

**Screening Measures**

Screenings and assessments were conducted by researchers with postgraduate level psychology qualifications. The MINI-International Neuropsyiatric Interview (MINI Plus) was used to screen participants for psychiatric disorders. The HAMA21 and Beck Anxiety Inventory (BAI)22 were used to assess the severity of anxiety symptomatology. Baseline depression levels were assessed with MADRS. Other screening measures included a drug and alcohol check questionnaire, current health and medications form, and a demographics questionnaire. A purpose-designed safety checklist was used to monitor any adverse effects and discontinuation symptoms (in week 7) of the treatment administered. This consisted of a tick-box list of common potential adverse effects, for example, digestive complaints. Three liver function blood tests (albumin, total protein, bilirubin, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase)25 were performed to determine current hepatic function and possible hepatotoxicity or abnormal liver function. These tests were conducted at baseline, then within the first few days of the control period, and finally during the final week of the control period. A blood sample was taken to analyze single nucleotide polymorphisms (SNPs) in the GABA (SLC6A1) and noradrenalin (SLC6A2) transporters. Specifically, GABA transporter SNPs rs2697153, rs2930152, rs1710879, rs2601126, and rs956053 and noradrenalin transporter SNPs rs3785157, rs11563824, rs998424, rs2242447, rs28386840, and rs2242446 were analyzed in the entire kava group (intention-to-treat or ITT) at the conclusion of the study. These SNPs were purposively selected because of previous studies finding links to either increased incidence of anxiety disorders or differing therapeutic effects of pharmacotherapies used for treating anxiety disorders. Polymorphisms were analyzed by Healthscope Pathology (Melbourne, Australia) from DNA extracted from whole blood using QiAmp mini-columns (Qiagen) according to the manufacturer’s instruction. Genotyping was then performed by single base extension assays and analyzed on the Sequenom Massarray.

**Procedure**

Participants were recruited in the greater Melbourne area in Victoria Australia, via the mass media (newspapers, television, and Internet). Advertising specified that the trial was testing kava for the treatment of anxiety. Initial screening was via a structured telephone interview. If they met inclusion criteria and
provided informed consent, participants were assessed on the MINI-Plus for the presence of social anxiety disorder, panic disorder, MDD, dysthymia, mania, or a psychotic disorder. They were administered a health and medication questionnaire, demographics questionnaire, a drug check form, HAMA, BAI, and MADRS and were asked to undergo a liver function and thyroid test within 3 days. Participants then commenced the first week of the study (placebo run-in phase), taking 1 placebo tablet twice per day (1 in the morning and 1 at night). One week later, they completed a safety checklist and were questioned regarding their adherence to treatment and the number of tablets remaining (which were retained for safe disposal). If an abnormality was revealed on their liver function test, they were informed that they were taking a placebo and were excluded from the trial. Otherwise, they were assessed again using the HAMA, MADRS, and BAI. If the HAMA showed a reduction of 50% or more from their baseline assessment, the participants were excluded from further participation and informed about alternative treatment opportunities. Eligible participants were then randomized to either 6 weeks of kava or placebo, concluding after this phase with a 1 week single-blinded placebo observation period. They were required to attend 6 sessions at a dedicated research suite at The Centre for Human Psychopharmacology in Melbourne Australia. Participants were compensated AUS $100 for travel expenses at the conclusion of the trial.

Statistical Analysis

A power calculation to determine the sample size was performed using Gpower 3.1.2. Given that the study is a blinded participants with GAD, a modest medium effect size for kava was postulated (F = 0.25, with an α probability of 0.05 and β power of 0.80). This provided a sample size of 78, with placebo response in the first week projected to exclude approximately 25%, a sample of 100 participants was estimated.

Reduction of anxiety score on the clinician-rated HAMA from baseline to study end point was the primary outcome measure, with the BAI being the secondary outcome measure. Data from all participants commencing week 1 (after placebo run-in) were included in analyses (ITT, with last observation carried forward). Results were examined with the substitution of missing data by the previous score: a conservative statistical method. Individual measures of anxiety were assessed for difference between baseline HAMA and end point (week 6) by repeated-measures analysis of variance: Treatment (kava and placebo) × Time (pretreatment, posttreatment). Genotyped SNPs and HAMA change were analyzed using the nonparametric Jonckheere-Terpstra test for ordered differences, whereas categorical data were analyzed via Pearson χ² test (or Fisher exact test for low cell counts). The significance level was set at P < 0.05 for anxiety and pharmacogenomic outcomes. We calculated the effect size (d) by taking the difference between means of the active and control groups at the start and end of the controlled phase and dividing this by the pooled within-group SD.26 Data were analyzed using SPSS (version 20; IBM). For further detail of the aims and design of the study, see Sarris et al.27

### RESULTS

#### Participant Characteristics

A total of 163 people were screened for the study, with 88 not being eligible for inclusion (not GAD, taking medication, comorbid depression, or nonconsent) (Table 1). A total of 75 participants met inclusion criteria and gave consent to participate in the 8-week study. After a 1-week placebo run-in, 9 participants were classified as “responders” (≥50% reduction on HAMA) and were excluded, 3 withdrew consent, 3 were re-diagnosed as not having GAD, and 2 were excluded because of a low HAMA score of less than 14. Thereby, data were available for ITT analysis from 58 adults meeting inclusion criteria who were randomized to treatment. Forty-eight participants completed the study, with no significant difference in dropout rates between groups. The mean (SD) age of participants across both groups included in the ITT analysis was 30.1 (8.8) years with a range of 19 to 60 years old. Twenty participants were male (56%), and 38 were female (65%). Thirty-one (54%) were single with 18 (31%) being married or partnered. Seven (12%) had high school level education, with 50 (86%) having studied at a university or postgraduate level. Thirty-three (57%) participants were in full-time or part-time education, whereas 14 (24%) were currently studying, and only 2 (3%) were unemployed. Fifty-three (91%) participants identified themselves as being of white ethnicity, with the other 5 (9%) having Asian ethnicity. After the 1-week placebo run-in phase, mean (SD) baseline scores for the sample were 20.5 (4.3) on the HAMA, 19.8 (8.7) on the BAI, and 11.7 (4.05) on the MADRS. DSM-IV diagnosis on the MINI-Plus for the severity of GAD revealed 9 (15%) participants as having mild, 34 moderate (59%), and 15 (26%) severe level symptoms. No significant between-group (kava and placebo) differences were found for any characteristic, signifying that the groups were homogenous.

Of the 58 randomized participants, at the end of the first 3-week control phase, 13 (45%) of the kava group and 16 (55%) of the placebo group did not respond and had their tablets titrated to a double dose. At the conclusion of the study, 54% of the kava group guessed that they were taking kava, whereas 57% of the placebo group guessed that they were taking placebo (χ², 0.47 = 1.73; P = 0.42). Compliance was rated by clinicians as good, with all participants taking more than 80% of prescribed doses as determined via tablet count.

#### Anxiety

A significant reduction in HAMA scores was observed in both groups for time (P < 0.0001), with a significant group × time interaction (F,1,55 = 4.16; P = 0.046) in favor of kava over placebo occurring. From baseline to the study end point, kava significantly reduced participant’s anxiety from (mean [SD]) 21.63 (4.2) to 14.03 (7.01) (−7.6 points) compared with 19.50 (4.2) to 15.26 (6.2) (−4.2 points) for placebo (Fig. 1), representing a moderate effect size (d = 0.63) in favor of kava.

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<th>TABLE 1. Participant Characteristics</th>
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*Fisher exact test.
Over one third (37%) of the kava group were classified as responders (≥50% HAMA reduction) compared with 23% of the placebo group ($\chi^2_{1,57} = 1.46; P = 0.23$). Approximately, a quarter (26%) of the kava group were classified as remitted (HAMA ≤ 7) compared with 6% of the placebo group ($\chi^2_{1,57} = 4.18; P = 0.04$).

For participants with moderate to severe level DSM-IV anxiety (as assessed on MINI Plus), the anxiolytic effect of kava was more pronounced ($F_{1,57} = 5.183; P = 0.020$), with a larger effect size ($d = 0.82$). When several potential a priori-determined covariates were applied in an analysis of covariance model, the effects were still significant when controlling for baseline MADRS depression ($P = 0.01$), baseline BAI anxiety ($P = 0.05$), thyroid function ($P = 0.02$), and weekly caffeine use ($P = 0.03$). Further subanalysis of participants with pure GAD and no other DSM-IV-diagnosed comorbid anxiety disorder (panic disorder, social phobia, posttraumatic stress disorder, obsessive-compulsive disorder), revealed a significant group × time interaction ($F_{1,25} = 6.19; P = 0.020; d = 1.28$), with a reduction of −8.5 points for kava on the HAMA compared with −2.3 points for placebo (Fig. 1). On the secondary outcome of BAI anxiety, both groups experienced a significant reduction of anxiety across time ($P < 0.0001$). Examination of BAI scores revealed a −3.2 point reduction in anxiety score in favor of kava ($d = 0.38$); however, this result was not significant.

**Genetic Correlates**

Of the 5 GABA transporter SNPs (rs2697153, rs2930152, rs1710879, rs2601126, and rs956053) studied, 2 (rs2697153 and rs2930152) were in perfect linkage disequilibrium ($r^2 = 1.0$; $D' = 1.0$); as such, we arbitrarily selected rs2697153 for further analysis. Analysis of the remaining 4 GABA transporter SNPs within the kava group showed that each SNP was significantly associated with reductions in HAMA scores, although rs1710879 ($P = 0.01$) and rs956053 ($P = 0.016$) were not in Hardy-Weinberg equilibrium ($P < 0.05$). Figure 2 shows a significant monotonic trend in which the number of rs2601126 T-alleles ($P = 0.021$) or rs2697153 A-alleles ($P = 0.046$) are associated with significant reductions in HAMA scores within the kava group. No significant associations were found for any of the noradrenalin transporter polymorphisms (data not shown).

**Safety Evaluation**

No major adverse reactions occurred during the study, whereas the only difference (with borderline significance) between kava and placebo concerned in 13 (48%) of 27 participants in the kava group experiencing headaches versus 7 (23%) of 30 ($\chi^2_{1,57} = 3.84; P = 0.05$) in the placebo group. However, no emergent headaches in individual participants were determined by the investigator to have likely occurred because of the tablets. For specific adverse effects noted by participants and determined by the investigator to be likely due to the tablets, these amounted...
to 1 case of allergy (placebo group), 1 case of dermatitis (kava), and 1 case of minor stomach upset (kava). Liver function tests at baseline, week 2 (1 week after the controlled intervention phase), and week 7 revealed no significant differences on any enzyme. The difference between the kava and the placebo groups of abnormal liver function tests showed 6 (24%) of 25 for kava versus 4 (17%) of 24 for placebo, with the result being nonsignificant ($\chi^2, 49 = 0.41; P = 0.73$). No participant in either group developed clinical signs of hepatic abnormality. Furthermore, the mean values of the liver function tests at all time points for both groups were well within standard range. The only trend for difference occurred for $\gamma$-glutamyl transferase being slightly raised in the kava group compared with placebo (baseline to study end point), with an increase of 3.8 in the kava group versus a reduction of 1.6 points in the placebo group ($F_{2,57} = 3.01, P = 0.08$). Overall, aspartate aminotransferase showed the opposite trend for differences between the groups with the placebo group being raised over time ($F_{2,57} = 2.74, P = 0.07$). During week 8 (placebo observation week), no significant withdrawal effects were noted for kava participants on any health domain, including neurologic, digestive, respiratory, or cardiovascular function (for further detail on the safety data cf. Sarris et al$^{[2]}$).

**DISCUSSION**

This study is the first completed double-blind RCT examining the efficacy of a standardized extract of kava in the treatment of GAD. The significant results and respectable effect sizes are of interest because GAD is a challenging condition to treat. Regardless, it should be noted that kava achieved a modest response rate of 37% (23%) in the placebo group, indicating it was not appreciably effective in most of the sample. This highlights the difficulty of treating GAD. The added novel finding of the study, concerning a possible association of specific genetic variants within the SLC6A1 locus encoding GABA transporter modify response, is intriguing: kava is known to affect genetic variants within the SLC6A1 locus encoding GABA transporters. The study found in the kava group versus a reduction of 1.6 points in the placebo group ($F_{2,57} = 3.01, P = 0.08$). Overall, aspartate aminotransferase showed the opposite trend for differences between the groups with the placebo group being raised over time ($F_{2,57} = 2.74, P = 0.07$). During week 8 (placebo observation week), no significant withdrawal effects were noted for kava participants on any health domain, including neurologic, digestive, respiratory, or cardiovascular function (for further detail on the safety data cf. Sarris et al$^{[2]}$).

Although our data show that kava is an effective anxiolytic, concerns over rare hepatotoxicity have led to its withdrawal or restriction in the European Union, United Kingdom, and Canada.$^{[28,30]}$ Kava extracts are, however, still currently available in the United States, Australia, and the South Pacific Islands. At the clinical level, a variety of case study data from patients with kava hepatotoxicity has been gathered,$^{[31]}$ and it appears to be an extremely rare occurrence with probable causation only directly linked in a few cases.$^{[32]}$ Causality assessment is complicated by various factors, including comorbid medical conditions and high drug and alcohol consumption in patients.$^{[33]}$ Present conjecture about the genesis of liver toxicity from kava extracts presently centers on the type of plant cultivars and solutes used and/or use of poor quality raw material.$^{[34]}$ In response to safety concerns, the World Health Organization commissioned a report assessing the risk of kava products.$^{[35]}$ Recommendations from this report suggest that products from water-based suspensions should be developed and tested in clinical studies and that these formulations should preferentially be used over acetonic and ethanolic extracts. The extract used in our research addresses these safety concerns by using a water-soluble, standardized formulation of kava from the peeled rootstock of a noble cultivar (such cultivars are higher in kawain and lower in dihydromethylcinn. It should be noted, however, that although no adverse reactions or hepatic issues have been found in any of our studies, it is possible that sample sizes are too small to conclusively support the extract’s safety; thus, further toxicologic and large epidemiological studies are required to firmly endorse its safe use.

Although current available evidence suggests that a standardized pharmaceutical-grade extract of kava (between 120 and 250 mg of kavalactones per day) may be an effective treatment for GAD, clinicians must consider a range of issues before prescribing. First, because of the differing quality of various kava extracts, efficacy and safety cannot currently be guaranteed for all kava products. Furthermore, clinicians need to be mindful of their patient’s liver function and current use of other medications if prescribing kava. Pharmacogenomic assessment of patient’s GABA transporters may provide a future novel indication of who is more likely to benefit from kava; however, this research would have to be replicated before this application could be firmly recommended.

Some limitations with the study are recognized. First, the study did not have a synthetic comparator such as an SSRI, and this treatment may have outperformed kava; second, although the genetics results reveal encouraging evidence, the results would not have been maintained after statistical correction for multiple comparisons. The sample size was not adequately powered to strongly confirm this finding (time and financial resources were exhausted and the target n of 100 was not reached); third, although participants were randomly assigned to groups, baseline HAMA anxiety for the kava group was by chance 2 points higher. It should be noted, however, that this difference was $P > 0.05$ and that results were maintained when adjusting for baseline anxiety, whereas all other characteristics were homogenous; fourth, because we used rigorous exclusion criteria, the results may not be generalizable to other populations such as those individuals with comorbid depression or those taking other psychotropic medication; fifth, because our advertising detailed the study of a “herbal treatment” for anxiety, this may have encouraged participation of biased individuals; last, the long-term efficacy and safety effects (ie, >6 months) of kava use in this population was not studied and remains an area of interest. In conclusion, our previous and current work shows that medically prescribed standardized kava (containing either 120, 240, or 250 mg of kavalactones) is a moderately effective short-term treatment for generalized anxiety, or DSM-diagnosed GAD, and our data tentatively suggest that response is modified by GABA transporter genetic variation. Future research involving another larger longer-term double-blind RCT is required to confirm these results, in addition to further observational safety studies.

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**AUTHOR DISCLOSURE INFORMATION**

The authors declare no conflicts of interest.
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