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Is Kava (Piper Methysticum) Safe and Effective for Reducing Anxiety in Adult Patients 18-65?

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Is Kava (piper methysticum) safe and effective for reducing anxiety in adult patients 18-65?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine is Kava (piper methysticum) safe and effective for reducing anxiety in adult patients 18-65?

STUDY DESIGN: Review of three English language primary randomized controlled studies published from 2005-2009.

DATA SOURCES: Randomized, double blind, placebo-controlled trials comparing Kava and placebo were found using OVID, PubMed, and CINAHL and COCHRANE databases.

OUTCOMES MEASURED: Each of the three trials assessed the adverse event of hepatotoxicity and clinical improvement in anxiety symptoms. Studies utilized to measure change in anxiety symptoms included State Trait Anxiety Inventory (STAI-state), Hamilton Anxiety Scale (HAMA), the Hospital Anxiety and Depression Scale (HADS), Sheehan Disability Inventory (SDI), and Beck Depression Inventory-II (BDI-II).

RESULTS: Three double-blind randomized controlled trials were included in this review. Results from the Conner et al study indicate that Kava use is effective in reducing anxiety in individuals with low baseline anxiety, but there were no differences between Kava and placebo when HAMA scores were $\geq$ 16 or $\geq$ 18. The second study by Sarris et al concluded that the response rate after treatment with Kava was 62% with a remission rate of 35%. The third study by Jacobs et al showed a reduction in anxiety symtpoms, but not greater than that of placebo; however, the data was not statistically significant. All three trials demonstrated that kava use does not contribute to hepatotoxicity.

CONCLUSIONS: All of the RCTs demonstrate that Kava use is safe and effective at reducing anxiety. However, it seems to be a less efficient option in the overall anxiety score reduction when compared to the current available treatment. In addition, the studies failed to demonstrate that Kava has an effect on hepatotoxicity.

KEY WORDS: Kava (piper methysticum), anxiety

INTRODUCTION

Anxiety is becoming an increasing health concern among the general population. It encompasses an extensive range of conditions including: post-traumatic stress disorder, obsessive compulsive disorder, panic disorder, phobias, and generalized anxiety disorder (GAD). It is the most common mental disorder that affects more than 18% of the U.S. population 18 years and older (40 million); GAD accounts for 6.8 million, or 3.1%.[1] By disrupting the central nervous system, specifically sympathetic response, anxiety leads to both psychological and physiological manifestations.[2] This paper evaluates three double blind, placebo-controlled, randomized controlled trials (RCTs), comparing the safety and efficacy of Kava for reducing generalized anxiety in adults.

Anxiety is relevant to the Physician Assistant profession due to its high rates of prevalence today. Half of all PAs work in a primary care setting, where GAD is very common, accounting for 3-8% of yearly office visits, (>6.8 million).[3,4] It accounts for almost one third of the total health expenses for mental illness, with an estimated $42 billion spent yearly. Additionally, anxiety sufferers are three to five times more likely to seek medical care and six times more likely to be hospitalized than those without anxiety.[1] Recent data shows that a quarter of the population will at some point experience anxiety that severely impacts their daily activities, including sleep, appetite, and thinking and are in need of prompt health professional advice.[5]

Although the exact cause of GAD is unknown, it is believed to be as a result of under-activation of serotoninergic and over-stimulation of noradrenergic neurotransmitters, as well as disturbance of the gamma-aminobutyric acid (GABA) system.[2] It is characterized by frequent, relentless worry and anxiety that is out of proportion to the situation for at least six months. [2,3]

Patients also often experience restlessness, fatigue, difficulty concentrating, irritability and muscle disturbances. The diagnosis of GAD is made based on history and DSM IV criteria. It can be rated by the Hamilton Anxiety Scale (HAMA) based on symptom severity, such as: behavior, anxious/depressed mood, fears, intellectual impairment, tension, insomnia cardiovascular, respiratory, GI, GU, autonomic, or somatic symptoms.[6]

Usual methods used to treat anxiety disorder include a combination of psychotherapy and pharmacotherapy. Cognitive Behavioral Therapy (CBT) has been proven to be most effective of the psychotherapies available, and when used in conjunction with medicine demonstrates to be twice as effective in establishing remission. Among the pharmacotherapy options, benzodiazepines are best in management of short-term symptoms and for those with severe impairment of function, in need of a quick-acting anxiolytic. However, due to their addiction and withdrawal potential, selective serotonin reuptake inhibitors (SSRIs) are the best-tolerated medications for long-term use. Given that SSRIs take 4-6 weeks to show symptom improvement, currently, the initial best treatment option includes a combination of benzodiazepines and SSRIs. [2]

The above regimens are effective treatment options for patients with anxiety, although most target multiple conditions and favorable effects and adverse reaction vary among each patient. Additionally, they may need to be used long-term in order to prevent relapse, which occurs in 25% of all patients within the first month of discontinuation, and in 60-80% over a year. Kava may be a natural anxiolytic alternative to these regimens in the reduction of anxiety and will be discussed further in this review.[2]

OBJECTIVE

The objective of this selective EBM review is to determine, "Is Kava (piper methysticum) safe and effective for reducing anxiety in adult patients 18-65?"

METHODS

The three studies utilized in this review were randomized controlled clinical trials and met the following criteria: The population consisted of adults ages 18-65 who met DSM-IV anxiety criteria. The intervention used was Kava 300mg, 280mg and 1,250mg. The treatment group receiving Kava was compared to the group receiving a virtually matched placebo. Outcomes measured included safety of Kava concerning drowsiness and hepatotoxicity and its' efficacy regarding anxiety.

Key words used to locate the literature consisted of Kava (piper methysticum) and anxiety. All articles were published in English and published in peer-reviewed journals. The articles were researched by the author and obtained via OVID, PubMed, CINAHL, and COCHRANE databases. Articles were selected based on relevance and significance of outcomes to the patients (POEMS). Inclusion criteria consisted of double blind, RCT studies, included patient oriented outcomes, and were published after 1996. Exclusion criteria included: patients under 18 years old, recent anxiety/depression treatment or disorder, substance abuse, breastfeeding, pregnancy, history of liver disease, lifetime history of bipolar disorder, psychiatric disorder, organic brain syndrome, or mental retardation. Statistics that were reported and utilized are relative risk (RR), relative risk reduction (RRR), absolute risk increase (ARI), absolute risk reduction (ARR), number needed to harm (NNH), number needed to treat (NNT), p-value, and χ^2-distribution.[7,8,9]

Demographics and characteristics of the studies utilized for this review are displayed in Table 1.

Table 1. Demographics and characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Jacobs[4], 2005	RCT	391	≥21 (mean: 41.4)	Adults who scored ≥ 40 points on STAI; ≥ 21 who reside in US and have access to email and WWW with anxiety documented by STAI 2 separate times	Pts who use sedative-hypnotic or benzos; drink >2 alcoholic drinks daily; hx of liver ds; pregnancy; breastfeeding	72	1) 1 100 mg Kava softgel capsule TID + 2 placebo valerian softgel capsules 1 hr before bed 2) 2 3.2 mg valerian softgel capsule 1 hour before bed + 1 placebo-Kava softgel capsule TID 3) Placebo-Kava + placebo-valerian softgel capsules
Connor[5], 2006	RCT	64	≥ 18 (mean: 52.5; 49.9; 43.6)	Adults with DSM-IV GAD – HAMA score of 16, 12-20, or 18 with symptoms for 6 mos	Hx of anxiety/mental ds; substance abuse; abnl lab/EKG; psychotropic tx, pregnancy; breastfeeding	N/A	1 70 mg Kava capsule BID x 1 week; then 1 140 mg Kava BID
Sarris[6], 2009	RCT	60	18-65 (mean: 44.4, 43.1)	Adults with at least 1 mo of persistent worry/anxiety scoring > 10 on BAI	Hx of bipolar psychosis; suicide ideation; substance abuse within 6 mo; use of antidepressant, benzos, or opiates in past 1 mo; concurrent psychological tx	19	5 250 mg Kava tabs QD x 3 weeks

OUTCOMES MEASURED

All outcomes measured in the trials were based on patient oriented evidence that mattered to the patients and assessed the adverse event of hepatotoxicity and clinical improvement in anxiety symptoms. Jacobs et al measured the change in anxiety symptoms based on the State subtest of the State Trait Anxiety Inventory (STAI-State) and reported adverse events throughout the study, including hospitalizations, ER visits, or any new symptoms or illnesses by contacting the on-call physician by e-mail or telephone.[7] The Conner et al study made assessments via the Hamilton Anxiety Scale (HAMA): scored 0 to 4, the Hospital Anxiety and Depression Scale (HADS), and the Sheehan Disability Inventory (SDI).[8] The Sarris et al study participants were assessed on the HAMA Scale, Beck Depression Inventory-II (BDI-II): 21 questions scored 0 to 3, and were asked to obtain liver function tests within 3 days.[9]

RESULTS

The results of two of the three trials, Jacobs et al and Connor et al, converted continuous data into dichotomous in order to assess the symptomatic improvement in anxiety and the safety of Kava use. The Sarris et al study used continuous data that could not be converted to dichotomous.

Connor et al study stratified participants based on the baseline entry criterion scores; it demonstrated that daily use of 280 mg Kavalactones titrated for a total of four week duration was effective in reducing generalized anxiety in individuals with low baseline anxiety (HAMA entry scores 12-20), yet no differences between Kava and placebo were found when HAMA scores were $\geq$ 16 or $\geq$ 18 with four and eight weeks of treatment, respectively (Table 2). Furthermore, the RRR was calculated to be 25% and the ARR was 5%. NNT was 20 patients and the p-value was determined to be statistically significant at $p<0.04$ and $p<0.05$ on the HAMA and HADS

assessments (Table 3). The NNT value indicates that for every 20 patients treated with 280 mg of Kava daily, one more patient would have complete remission of anxiety than if treated with placebo. In addition, in this limited sample, Kava use appeared safe with respect to liver function, with all values remaining well below the normal reference range (Table 4).

Table 2. Baseline entry criteria and symptom severity before and after treatment

Study	Treatment Duration	Patients (*n*)	Entry Criteria	Before	After	Anxiety Reduction *
HAMA Trial 1	4 weeks	35	Baseline HAMA $\geq$ 16	Kava: 21 Placebo: 18	Kava: 13 Placebo: 10	Kava: 8 Placebo: 8
HAMA Trial 2	4 weeks	13	Baseline HAMA 12-20	Kava: 17 Placebo: 14	Kava: 7.5 Placebo: 10	Kava: 9.5 Placebo: 4
HAMA Trial 3	8 weeks	16	Baseline HAMA $\geq$ 18	Kava: 32 Placebo: 24	Kava: 20 Placebo: 12	Kava: 12 Placebo: 12

HAMA: Hamilton Anxiety Scale

* Points reduction in HAMA score before and after treatment with Kava and placebo

Table 3. Analysis of efficacy of Kava use for remission of generalized anxiety.

Study	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Number needed to treat (NNT)	p-value
Connor[5], 2006	25%	5%	20 patients	HAMA: $p<0.04$ HADS: $p<0.05$

Table 4. [8]
Comparison of liver enzyme scores after treatment with Kava and placebo (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

Sarris et al study started with 182 volunteers, 141 of who were excluded due to no stable anxiety symptoms, use of antidepressants or anti-anxiety medication, bipolar depression, liver dysfunction, high alcohol or drug use, and positive placebo response. The primary result outcomes were measured via HAMA with secondary outcomes measured by the BAI scale after administration of 250 mg of Kava daily for a total of three weeks. The HAMA scale showed statistically significant ($p<0.0001$) results where anxiety was reduced by -9.9 points (CI = -12.7, -7.1) below pretreatment levels during the first controlled trial and by -10.3 (CI = -14.7, -5.8) points during the second trial, compared with a -0.8 (CI = -4.3, +2.7) decrease with placebo use during trial one, and an increase of +3.3 (CI = -0.2, +6.8) points in trial two. The BAI scale also revealed statistically significant data ($p=0.001$) in support of Kava, with reduction by -7.2 (CI = -10.8, -3.5) points and -8.1 (CI = -12.5, -3.6) for trial one and two, respectively. Placebo use in trial one showed a -1.6 (CI = -5.6, +2.5) point reduction, and an increase of +1.4 (CI = -2.0, +4.9) points in trial two (Table 5). In addition, serious adverse effects, including hepatotoxicity were not evident in either trial based on participant reporting. Furthermore, the study concluded that the response ($\geq$ 50% reduction below baseline on HAMA) rate after treatment with Kava was 62% with a remission rate of 35%. [9]

Table 5. Symptom severity before and after treatment with Kava and placebo.[9]

	Mean (SD)			
Outcome measure	**Pretreatment score (SD)**	**Trial 1**	**Trial 2**	***p***
HAMA	KP 21.16 (3.52) PK 20.28 (4.78)	KP 11.26 (4.47) PK 19.50 (7.26)	KP 14.58 (5.86) PK 9.22 (5.96)	<0.0001
BAI	KP 16.47 (4.90) PK 17.94 (5.98)	KP 9.32 (6.49) PK 16.39 (10.16)	KP 10.74 (6.04) PK 8.33 (7.39)	0.001

KP: Kava week 1, Placebo week 2; PK: Placebo week 1, Kava week 2

Jacobs et al converted continuous data into dichotomous for NNH, but no dichotomous data was provided for NNT. To determine effectiveness in anxiety reduction, symptom severity

was assessed using the STAI scale. Participants who received four weeks of Kava therapy had a total reduction in anxiety of -11.8, whereas those on placebo had a reduction of -14.4 (Table 6). However, this difference between groups is +2.7 with a 95% CI (-0.8, +6.2) and is not statistically significant. All participants were contacted either by e-mail or postal mail concerning hepatotoxicity, since this study was conducted before safety warnings were issued; none of the participants reported any adverse events. Additionally, side effects of similar frequency occurred between Kava and placebo groups.[7] In regards to headache and drowsiness, the RRI was calculated to be 21% and ARI -5%. NNH was -20 patients at a confidence interval of 95%. The negative value of NNH shows that for every 20 patients treated with Kava, one fewer patient would experience headache or drowsiness when compared to placebo.

Table 6. Symptom severity before and after treatment with Kava and placebo.

	Mean (SD)		
Outcome measure: STAI	**Kava (n=121)**	**Placebo (n=135)**	**Kava – Placebo (95% CI)**
Baseline	56.8 (9.6)	56.6 (9.3)	
Week 2 – change from baseline	-9.2 (9.9)	-11.1 (11.4)	
Week 4 – change from baseline	-11.8 (12.3)	-14.4 (12.9)	+2.7 (-0.8 to +6.2)

STAI: State-Trait Anxiety Inventory

Table 7.
Analysis of safety of Kava use regarding headache and drowsiness for generalized anxiety.

Study	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)	CI
Jacobs[4], 2005	- 21%	- 5%	-20 patients	95%

DISCUSSION

Kava is a native plant found in the South Pacific and has many reported uses, including those for anxiety, insomnia, skeletal muscle relaxation, and ADD/ADHD in children. Its use as an anxiolytic is becoming more popular, especially in Western Europe for the treatment of

anxiety and nervous tension. It works by exerting its effects on the amygdala in the limbic system, which is responsible for generation of emotion.[8,10] Currently, the FDA is trying to ascertain Kava's effects on hepatotoxicity and the safety of its use. Presently, it is contraindicated in pregnancy and lactation, as well as Parkinson's disease due to it's potential dopamine antagonistic effects.[10]

As a result of hepatotoxicity, Kava use has been banned in the United States. However, Kava use in regards to hepatotoxicity has been proven safe; the toxicity patterns that had seemed to emerge may be as a result of difference in genetics and human metabolism. In addition, the preparations used to make kava tablets, such as ethanol and the use of kava stems and leaves as opposed to only the root extract is what had lead to hapatotoxicity and the current ban. Moreover, studies have shown that Kava inhibits cytochrome isoenzymes 1A2, C29, 2C19, 2D6, and 3A4 and concomitant use with other medications could lead to hepatotoxicity. Newer formulations of Kava, which exclude methysticin and dihydromethysticin may lead to developments of a safer form of Kava.[8] Additionally, Kava side effects were comparable to and possibly even superior to most benzodiazepine trials and did not demonstrate any withdrawal effects upon discontinuation, as can be seen with benzodiazepines and SSRIs.[8,9]

Connor and Sarris et al studies showed a decrease in anxiety scores when compared to placebo, while the Jacobs et al study shows Kava reduces symptoms of anxiety but not greater than that of placebo. Although data in this review supports the use of Kava in reduction of anxiety, not all of the data presented is clinically significant. Even though the three studies provide adequate data, the small sample size may not be adequately large enough to show a difference in treatment such as that of the Conner et al study that only shows effectiveness among 13 participants with low base-line anxiety (HAMA score 12-20). In addition, this

reduction may not be clinically significant enough to therapeutically be beneficial to patients with generalized anxiety.

Certain limitations to the studies exist and many factors may have affected the outcome. One of the factors is that participants have strong beliefs in the efficacy of natural alternatives, which may have influenced response to treatment, thereby not showing a difference in Kava use versus placebo. Limitations of the studies include: less consistent responses from patients that used the internet for responses, resulting in misleading information; small sample sizes; differences regarding duration of GAD prior to study entry and duration of treatment; and the average patient population (50 years) is higher than the average age of participants with GAD.[7,8,9]

CONCULSION:

Kava has been proven to be safe and effective at reducing anxiety in adults 18-65. However, considering the inconsistencies and inconclusiveness of the data, other therapies may be more beneficial at this time with pending FDA studies, which are thereby limiting further research in the US currently. Therefore, it can be concluded that Kava therapy alone is a less efficient treatment option, but is still successful in reducing anxiety with comparable side effects to other available options. Further studies can refine the population of interest by setting a more narrow age-requirement range; for example: 18-25; 26-33; 34-41; 42-50; 51-60. By targeting a smaller population in similar age groups, the population better relates to one another and anxiety and stress response at study initiation will not be as varied. Future studies can also do a pre and post liver enzyme study among all participants to get a better understanding of hepatotoxicity.

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