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[Intervention Review]

Kava extract versus placebo for treating anxiety

Max H Pittler[1], Edzard Ernst[2]

[1]German Cochrane Center, Department of Medical Biometry and Statistics, Freiburg, Germany. [2]Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK

Contact address: Max H Pittler, German Cochrane Center, Department of Medical Biometry and Statistics, University Medical Center Freiburg, Berliner Allee 29, Freiburg, 79110, Germany. pittler@cochrane.de, max.pittler@pms.ac.uk.

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ABSTRACT

Background

Constraints on resources and time often render treatments for anxiety such as psychological interventions impracticable. While synthetic anxiolytic drugs are effective, they are often burdened with adverse events. Other options which are effective and safe are of considerable interest and a welcome addition to the therapeutic repertoire.

Objectives

To assess the effectiveness and safety as reported in rigorous clinical trials of kava extract compared with placebo for treating anxiety.

Search methods

All publications describing (or which might describe) randomised, double-blind, placebo-controlled trials of kava extract for anxiety were sought through electronic searches on EMBASE (1974 to January 2005), MEDLINE (1951 to January 2005), AMED (1985 to January 2005)), CISCOM (inception until August 2002) and Central/CCTR and CCDANCTR (issue 1, 2005). The search terms that were used were kava, kawa, kavain, Piper methysticum and Rauschpfeffer (German common name for Piper methysticum). Additionally, manufacturers of kava preparations and experts on the subject were contacted and asked to contribute published and unpublished material. Hand-searches of a sample of relevant medical journals (Erfahrungsheilkunde 1996 - 2005, Forsch Komplementärmed Klass Naturheilkd 1994 - 2005, Phytomed 1994 - 2005, Alt Comp Ther 1995 - 2005), conference proceedings (e.g. FACT - Focus on Alternative and Complementary Therapies 1996 - 2005) and our own collection of papers were conducted. No restrictions regarding the language of publication were imposed.

Selection criteria

To be included studies were required to be randomised, controlled trials (RCTs), i.e. trials with a randomised generation of allocation sequences, and conducted placebo-controlled and double-blind, i.e. trials with blinding of patients and care providers. Trials using oral preparations containing kava extract as the only component (mono-preparation) were considered. Trials using single constituents of kava extract alone, assessing kava extract as one of several active components in a combination preparation or as a part of a combination therapy were excluded.

Data collection and analysis

Data were extracted systematically according to patient characteristics, interventions and results. Methodological quality of all trials was evaluated using the standard scoring system developed by Jadad and colleagues. The screening of studies, selection, data extraction, validation and the assessment of methodological quality were performed independently by the two reviewers. Disagreements in the evaluation of individual trials were largely due to reading errors and were resolved through discussion.

Main results

Twelve double-blind RCTs (n=700) met the inclusion criteria. The meta-analysis was done on seven studies using the total score on the Hamilton Anxiety (HAM-A) scale as a common outcome measure. The result suggests a significant effect towards a reduction of the HAM-A total score in patients receiving kava extract compared with patients receiving placebo (weighted mean difference: 3.9, 95% confidence interval: 0.1 to 7.7; p = 0.05; n = 380). The results of the five studies that were not submitted to meta-analysis largely support these findings. Adverse events as reported in the reviewed trials were mild, transient and infrequent.

Authors' conclusions

Compared with placebo, kava extract is an effective symptomatic treatment for anxiety although, at present, the size of the effect seems small. The effect lacks robustness and is based on a relatively small sample. The data available from the reviewed studies suggest that kava is relatively safe for short-term treatment (1 to 24 weeks), although more information is required. Rigorous trials with large sample sizes are needed to clarify the existing uncertainties. Also, long-term safety studies of kava are required.

PLAIN LANGUAGE SUMMARY

Kava extract for treating anxiety

Systematic literature searches were conducted to assess the evidence for or against the effectiveness of kava extract for treating anxiety. Twenty-two potentially relevant double-blind, placebo-controlled RCTs were identified. Twelve trials met the inclusion criteria. The meta-analysis of seven trials suggests a significant treatment effect for the total score on the Hamilton Anxiety Scale in favour of kava extract. Few adverse events were reported in the reviewed trials, which were all mild, transient and infrequent. These data imply that, compared with placebo, kava extract might be an effective symptomatic treatment for anxiety although, at present, the size of the effect seems to be small. Rigorous trials with large sample sizes are needed to clarify the existing uncertainties. Particularly long-term safety studies of kava are needed.

BACKGROUND

Anxiety disorders commonly occur, seriously impair mental health (Myers 1984), and are of considerable importance in terms of economic burden to society. Data from the United States National Comorbidity Survey suggests a one-year prevalence of 17% and a lifetime prevalence of almost 25% (Kessler 1994), while annual costs of anxiety disorders have been estimated at approximately $42.3 billion in 1990, which is equivalent to about $1542 per patient (Greenberg 1999). In the majority of cases, patients are treated by general practitioners (Walley 1994, Robinson 1993; Deans 1992) and benzodiazepines are commonly used. However, these are associated with adverse events, which include dependence, sedation and memory impairment (Priest 1988; Gorman 1990; Hunt 1991). Constraints on resources and time often render other treatments such as psychological interventions impracticable. Data from a nationally representative survey conducted in the United States suggest that anxiety patients frequently use complementary and alternative therapies (Kessler 2001; Astin 1998) and one possible option is kava extract (Brevoort 1998).

Kava is the beverage prepared from the rhizome of the kava plant (Piper methysticum Forst.) (Cawte 1985). Throughout the South Pacific extracts of kava have been used for recreational and medicinal purposes. Traditionally, it was used to treat a variety of ailments such as gonorrhoea and to induce relaxation and sleep but also to counteract fatigue (Lebot 1992; Singh 1998). The rhizome of cultivated P. methysticum is used as raw material for the production of kava extract (Habs 1994). In 1998, it was among the top selling herbs in the US totalling approximately $8 million in annual retail sales (Brevoort 1998). In 2000, this had increased to approximately $15 million (Blumenthal 2001). Uncontrolled clinical studies have suggested that kava may be beneficial for treating anxiety (e.g. Melville 1964; Lemert 1967). Data from a previous review confirmed these early findings and suggested a significant reduction of the Hamilton-Anxiety (HAM-A) total score of 9.7 points in favor of kava compared with placebo (Pittler 2000a). The exact mechanism of action of kava is unclear. New data from randomised, controlled trials (RCTs) have become available, which prompted us to update this Cochrane review.

OBJECTIVES

To assess the effectiveness and safety as reported in rigorous clinical trials of kava extract compared with placebo for treating anxiety.

METHODS

Criteria for considering studies for this review

Types of studies

To be included studies were required to be RCTs, i.e. trials with a randomised generation of allocation sequences, and conducted placebo-controlled and double-blind, i.e. trials with blinding of patients and care providers .

Types of participants

Trial participants had to be patients, who were suffering from anxiety.

Types of interventions

Trials using oral preparations containing kava extract as the only component (mono-preparation) were considered. Trials using single constituents of kava extract alone, assessing kava extract as one of several active components in a combination preparation or as a part of a combination therapy were excluded.

Types of outcome measures

Trials assessing clinical outcome measures related to anxiety (e.g.Hamilton Anxiety scale) were included. Of primary interest is the change of baseline to post treatment data. Data on the safety of kava are described as they were reported in the reviewed trials.

Search methods for identification of studies

See: Collaborative Review Group search strategy.
All publications describing (or which might describe) randomised, double-blind, placebo-controlled trials of kava extract for anxiety were sought through electronic searches. Databases were searched from their inception: EMBASE (1974 to January 2005), MEDLINE (1951 to January 2005), AMED (1985 to January 2005)), CISCOM (Research Council for Complementary Medicine, London; until August 2002) and Central/CCTR and CCDANCTR (Cochrane Collaborative Depression, Anxiety & Neurosis Controlled Trials register) on the Cochrane Library (issue 1, 2005).

The search terms that were used were kava, kawa, kavain, Piper methysticum and Rauschpfeffer (German common name for Piper methysticum). Manufacturers of kava preparations and experts on the subject were contacted and asked to contribute published and unpublished material.

Hand-searches of a sample of relevant medical journals (Erfahrungsheilkunde 1996 - 2005, Forsch Komplementärmed Klass Naturheilkd 1994 - 2005, Phytomed 1994 - 2005, Alt Comp Ther 1995 - 2005), conference proceedings (e.g. FACT - Focus on Alternative and Complementary Therapies 1996 - 2005) and our own collection of papers were conducted.

The bibliographies of all papers located were searched for further trials. No restrictions regarding the language of publication were imposed.

Data collection and analysis

Study selection

The screening of studies, selection, data extraction, validation and the assessment of methodological quality were performed independently by the two reviewers.

Data extraction

Articles in languages other than English or German were translated in-house. Data were extracted systematically according to the methods used, outcome measures, patient characteristics, interventions, results and adverse events.

Assessment of methodological quality

Methodological quality was evaluated using the scoring system developed by Jadad and colleagues (Jadad 1996), which quantifies the likelihood of bias inherent in the trials, based on the description of randomisation, blinding and withdrawals. Disagreements in the

evaluation of trials were largely due to reading errors and were resolved through discussion.

Data analysis

Meta-analysis was performed using standard meta-analysis software (RevMan 4.2.7, Update Software Ltd., Oxford, England). It uses the inverse of the variance to assign a weight to the mean of the within-study treatment effect. For most studies, however, the information was insufficient to allow us to directly calculate the variance of the pre-intervention to post-intervention change. The Cochrane Collaboration suggests to impute the variance of the change by assuming a correlation factor of 0.4 between pre-intervention and post-intervention values. The variance of the change was imputed using this correlation factor and then used to assign a weight to the mean of the within-study treatment effect. In addition, further information was sought through contacting the authors of the original trials and the manufacturer of the preparations that were used. The meta-analysis was performed using the weighted mean difference.

The treatment effect was calculated using a random effects model. The chi-square test for heterogeneity tested whether the distribution of the results was compatible with the assumption that inter-trial differences were attributable to chance variation alone.

Sensitivity analyses were performed post-hoc to test the robustness of the main analysis. For the meta-analyses the data were re-calculated based on the original raw data except for Conn 2001.

RESULTS

Description of studies

For this update, one new study was identified (Connor 2002). Previously unpublished trials are now published (Gastpar 2003; Geier 2004; Lehrl 2004). In total, twenty-two potentially relevant double-blind, placebo-controlled RCTs were identified (Lehmann 1998; Lehmann 1996; Lehmann 1989; Lindenberg 1990; Bhate 1992; Bhate 1989; Möller 1992; Möller 1989; Staedt 1991; Malsch 2001; Kinzler 1991; Warnecke 1991; Warnecke 1990; Warnecke 1986; Warnecke 1989; Volz 1997; Singh 1998; De Leo 2001; Geier 2004; Lehrl 2004; Gastpar 2003; Connor 2002). Two studies were duplicate publications (Lehmann 1996; Bhate 1992), eight others were excluded because they were either not performed with a kava extract monopreparation (Warnecke 1989; Warnecke 1986), were performed as part of a combination therapy (De Leo 2001) or were performed using kavain (Möller 1992; Möller 1989; Lehmann 1989; Staedt 1991; Lindenberg 1990). Twelve double-blind, placebo-controlled RCTs met all inclusion criteria and were reviewed. Seven trials assessed a common outcome measure and provided data, which were suitable for meta-analysis (Geier 2004; Lehrl 2004; Connor 2002; Malsch 2001; Volz 1997; Kinzler 1991; Warnecke 1991). All, except one (Connor 2002), used the same preparation (WS1490), which is standardised to 70 % kavalactone content and is produced by the same manufacturer. Key data from all included trials are presented in the characteristics of included trials table.

Risk of bias in included studies

Six trials scored the maximum of 5 points on the Jadad scale (Jadad 1996). Four of seven trials that could be included in the meta-analysis scored the maximum of 5 points, while three other trials lacked either a description of randomization procedures (Lehrl 2004; Malsch 2001) or lacked a description of randomization and double-blinding procedures (Volz 1997).

Effects of interventions

A total of twelve double-blind RCTs (n=700) were reviewed (Characteristics of included studies table). Six trials reported adverse events experienced by patients receiving kava extract. Stomach complaints, restlessness, drowsiness, tremor, headache and tiredness were reported most frequently. Four trials comprising 30% of patients in the reviewed trials report the absence of adverse events while taking kava extract. None of the trials reported any hepatotoxic events. Seven of the reviewed trials (Gastpar 2003; Geier 2004; Lehrl 2004; Conn 2001 reported in Connor 2001; Malsch 2001; Volz 1997; Warnecke 1991) measured liver enzyme levels as safety parameters and report no clinically signifcant changes.

Data from seven trials (n=380) assessed a common outcome measure - the total score on the HAM-A scale - and were included in the meta-analysis (Lehrl 2004; Geier 2004; Connor 2002; Malsch 2001; Volz 1997; Kinzler 1991; Warnecke 1991). 74 % of these patients (n = 282) were diagnosed according to the criteria of the American Psychiatric Association (DSM-III-R, DSM-IV). All trials used the HAM-A total score at baseline as an inclusion criterion and four trials included patients if the total score was 19 or above (Characteristics of included studies table). The result of the meta-analysis suggests an effect towards a reduction of the HAM-A total score in patients receiving kava extract compared with patients receiving placebo (weighted mean difference: 3.9, 95% confidence interval: 0.1 to 7.7; p = 0.05; n = 380). The chi-square test indicated heterogeneity (chi square = 27.5; p = 0.0001). Visual inspection of the forest plot identified two outlier (Connor 2002; Warnecke 1991), which were mainly responsible for the heterogeneity. Warnecke 1991 was the only one that included only women with anxiety due to climacteric syndrome. Connor 2002 was the only trial that did not use the kava preparation WS1490. Other potential sources of clinical heterogeneity (dose of kava, duration of treatment, degree of baseline severity or setting) could not be identified (Characteristics of included studies table). Removing these trials and pooling the data of the remaining five trials (chi square = 9.0; p = 0.06) suggests a significant reduction of the HAM-A total score in patients receiving kava extract compared with patients receiving placebo (weighted mean difference: 3.4, 95% confidence interval: 0.5 to 6.4; p = 0.02; n = 305).

Other sensitivity analyses testing the robustness of the main analysis assessed whether including only the data of patients with non-psychotic anxiety diagnosed according to the criteria of the American Psychiatric Association (DSM-III-R, DSM-IV) criteria (Geier 2004; Lehrl 2004; Connor 2002; Malsch 2001; Volz 1997) would alter the direction of the result. The meta-analysis of these data (chi square = 5.8; p = 0.2) suggests a non-significant effect (weighted mean difference: 1.0, 95% confidence interval: -1.3 to 3.3; p = 0.4; n = 282). The analysis of trials assessing outpatients with non-psychotic anxiety patients and a HAM-A total score of 19 or above (Geier 2004; Kinzler 1991; Volz 1997) who received 200 to 210 mg kavalactones daily (chi square = 7.7; p = 0.02) indicated a non-significant trend (weighted mean difference: 4.5, 95% confidence interval: -0.6 to 9.7; p = 0.08; n = 208).

The results of the five studies that were not submitted to meta-analysis largely support these findings (see characteristics of included studies). Singh 1998 reported a reduction in favour of kava compared with placebo for the State-Trait Anxiety Inventory. Two studies reported a reduction on the Zung Anxiety Status Inventory (Gastpar 2003; Warnecke 1990), whereas Bhate 1989 reported a reduction compared with placebo on a 10-Item Anxiety Scale. Lehmann 1998 assessed the responder-non-responder ratio and found a differential effect in favour of kava.

DISCUSSION

The addition of one new trial (Connor 2002) has reduced the effect by one point on the HAM-A total score, which is of borderline statistical significance. Thus, compared with placebo, kava extract might be an effective symptomatic treatment for anxiety although, at present, the size seems to be small. The effect lacks robustness as indicated by the sensitivity analyses and is based on a relatively small sample. Nonetheless, the reviewed trials which could not be included in the meta-analysis support the findings and suggest that kava is beneficial for patients with anxiety when compared with placebo. This is corroborated by the results of comparative trials (Boerner 2003) other systematic reviews (Jorm 2004) and previous reviews (Singh 1998; Weber 1994; Chrubasik 1997; Hänsel 1996). However, larger rigorous trials, particularly in long-term studies, are needed.

In our own systematic review assessing the safety of kava (Stevinson 2002), two drug monitoring studies of kava were located. They included a total of 7078 patients taking kava extract equivalent to 105 mg to 240 mg kavalactones per day for 5 to 7 weeks. In these studies no cases of hepatotoxicity emerged, which is supported by a further study (Connor 2001). Two other postmarketing surveillance studies, including 1673 patients who received kava extract equivalent to 120 mg kavalactones daily for 5 weeks (Spree 1992) and 2944 other patients who received 400 mg kavain daily for 4 weeks (Unger 1988) corroborate this and report no hepatotoxic events. Indeed, kava hepatotoxicity seems to be a very rare event (Teschke 2003; Schulze 2003). No plausible mechanism for the alleged hepatotoxic effects of kava has so far been identified. The question therefore remains whether the frequency of liver damage in kava users differs significantly from that of non-kava users.

Limitations of this meta-analysis pertain to the citation tracking and its potential incompleteness. Although strong efforts were made to locate and retrieve all trials on the subject, it is conceivable that some were not uncovered. The distorting effects on systematic reviews arising from publication bias and location bias are well-documented (Easterbrook 1991; Egger 1998). There are also suggestions that positive findings may be overrepresented in complementary medicine journals (Ernst 1997; Schmidt 2001, Pittler 2000b). In addition, there is evidence for the tendency of positive findings to be published in English language journals (Egger 1997) and for some European journals to not be indexed in major medical databases (Nieminen 1999). Therefore the possibility of treatment effects to be exaggerated exists, which may be particularly relevant to herbal medicinal products where much of the evidence originates from European countries. Databases searched for the purposes of this study included those with a focus on the American and European literature and those that specialize in complementary medicine. There were no restrictions in terms of publication language. We are therefore confident that this strategy has minimized bias in the present study.

Other pharmacological options include antidepressants and benzodiazepines. The latter, however, may cause adverse events such as sedation, amnesia, developement of tolerance and carry an increased risk of road-traffic accidents (Barbone 1998; Moore 1998; O'Neill 1998). Comparative studies that were identified during the searches suggest the absence of significant differences between benzodiazepines and kavain or kava extract (Lindenberg 1990; Woelk 1993) in terms of effectiveness. However, a systematic assessment is required for firm statements. Also, more equivalence studies are needed, not least to define the relative risks of both approaches.

AUTHORS' CONCLUSIONS

Implications for practice

Compared with placebo, kava extract is an effective symptomatic treatment for anxiety although, at present, the size of the effect seems to be small. The effect lacks robustness and is based on a relatively small sample. The data available from the reviewed studies suggest that kava is relatively safe for short-term treatment (1 to 24 weeks), although more information is required.

Implications for research

Rigorous trials with large sample sizes are needed to clarify the existing uncertainties. Also, long-term safety studies of kava are required.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bhate 1989

Methods	Randomised, placebo-controlled double-blind; 2 parallel groups
Participants	Pre-operative patients (n=59); General hospital, Germany
Interventions	300 mg (60 mg kavalactones) night before operation and 300 mg (60 mg) 1 hour before operation
Outcomes	10-Item Anxiety Scale. Differential reduction of anxiety in favour of kava (p<0.05)
Notes	Adverse events (kava group): postoperative hangover Jadad score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Connor 2002

Methods	Randomised, placebo-controlled double-blind; 2 parallel groups
Participants	Outpatients with generalized anxiety disorder (DSM-IV) ; HAMA total score 16 or above (per-protocol; n=35); University outpatient setting, US
Interventions	140 mg kavalactones daily for 1 week, then 280 mg kavalactones daily for 3 weeks
Outcomes	HAM-A total score. Mean difference, 95% confidence interval -2.8; -5.4 to -0.2
Notes	'No evidence of withdrawal or sexual side effects' Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gastpar 2003

Methods	Randomised, placebo-controlled double-blind, multicenter; 2 parallel groups
Participants	Outpatients with neurotic anxiety (DSM-III-R) ; HAMA total score 19 or above (intention-to-treat; n=141); 17 general practices in Germany
Interventions	50 mg 3 times (105 mg kavalactones) daily for 4 weeks
Outcomes	Zung Anxiety Status Inventory. Reduction compared with baseline in kava group (p<0.001)

Gastpar 2003 *(Continued)*

Notes	Adverse events (kava group): tiredness, symptom aggravation, unrelated to the investigational treatment (not detailed), Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Geier 2004

Methods	Randomised, placebo-controlled double-blind; 2 parallel groups
Participants	Patients with nonpsychotic anxiety (DSM-III-R) ; HAMA total score 19 or above (intention-to-treat; n=50); Hospital setting, Germany
Interventions	50 mg 3 times (105 mg kavalactones) daily for 4 weeks
Outcomes	HAM-A total score. Mean difference, 95% confidence interval 0.4; -3.5 to 4.3
Notes	Adverse events (kava group): Pleuro pneumonia; deterioration of pre-existing pulmonary fibrosis Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kinzler 1991

Methods	Randomised, placebo-controlled double-blind; 2 parallel groups
Participants	Outpatients with nonpsychotic anxiety syndrome (ICD 9); HAMA 19 or above (intention-to-treat; n=58); University outpatient setting, Germany
Interventions	100 mg 3 times (210 mg kavalactones) daily for 4 weeks
Outcomes	HAM-A total score. Mean difference, 95% confidence interval 8.7; 4.3 to 13.1
Notes	Adverse events (kava group): none Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lehmann 1998

Methods	Randomised, placebo-controlled double-blind;2 parallel groups
Participants	Pre-operative women (n=20); University hospital, Germany
Interventions	150 mg 3 times (150 mg kavalactones) daily for 1 week
Outcomes	Responder - non-responder ratio. Differential reduction of anxiety in favour of kava (p<0.05)
Notes	Adverse events (kava group): not detailed Jadad score: 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lehrl 2004

Methods	Randomised, placebo-controlled double-blind, multicenter; 2 parallel groups
Participants	Patients with sleep disturbances associated with nonpsychotic anxiety (DSM-III-R) ; HAMA total score 16 or above (intention-to-treat; n=57); 3 centers in Germany
Interventions	200 mg once (140 mg kavalactones) daily for 4 weeks
Outcomes	HAM-A total score. Mean difference, 95% confidence interval 1.4; -3.4 to 6.2
Notes	Adverse events (kava group): none Jadad score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Malsch 2001

Methods	Randomised, placebo-controlled double-blind; 2 parallel groups
Participants	Outpatients with nonpsychotic anxiety and pretreatment with benzodiazepines (DSM-III-R); HAMA total score of 14 or below (median at baseline: 13 kava / 13 placebo; intention-to-treat; n=40); General Hospital, Hamburg, Germany
Interventions	Tapering off benzodiazepines and increase from 50 to 300 mg (210 mg kavalactones) daily for 1 week. Then 100 mg 3 times daily for 3 weeks.
Outcomes	HAM-A total score. Mean difference, 95% confidence interval 2.4; -1.5 to 6.3
Notes	Adverse events (kava group): not detailed Jadad score: 4

Malsch 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Singh 1998

Methods	Randomised, placebo-controlled double-blind; 2 parallel groups
Participants	Patients with anxiety diagnosed using the State Trait Anxiety Inventory (n=60); University setting, US
Interventions	400 mg 2 times (240 mg kavalactones) daily for 4 weeks.
Outcomes	State-trait Anxiety Inventory. Differential reduction in favour of kava (p<0.0001); no differential effect for trait anxiety
Notes	Adverse events (kava group): none Jadad score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Volz 1997

Methods	Randomised, placebo-controlled double-blind, multicenter; 2 parallel groups
Participants	Outpatients with nonpsychotic anxiety (DSM-III-R); HAMA total score 19 or above (intention-to-treat; n=100); General practice, Germany
Interventions	100 mg 3 times (210 mg kavalactones) daily for 24 weeks
Outcomes	HAM-A total score. Mean difference, 95% confidence interval 4.8; -0.6 to 10.2
Notes	Adverse events (kava group): not detailed; stomach upset were rated by the investigators as possibly related to the intake of kava Jadad score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Warnecke 1990

Methods	Randomised, placebo-controlled double-blind; 2 parallel groups

Warnecke 1990 *(Continued)*

Participants	Female outpatients with anxiety due to climacteric syndrome (n=40); Gynaecology practice, Germany
Interventions	150 mg 2 times (60 mg kavalactones) daily for 4 weeks
Outcomes	Zung Anxiety Status Inventory. Reduction compared with baseline in kava group (p<0.001); no effect in placebo group
Notes	Adverse events (kava group): headache, tiredness and lack of energy; stomach complaints, heartburn and diarrhoea Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Warnecke 1991

Methods	Randomised, placebo-controlled double-blind; 2 parallel groups
Participants	Female outpatients with anxiety due to climacteric syndrome; HAMA total score 19 or above (intention-to-treat; n=40); Gynaecology practice, Germany
Interventions	100 mg 3 times (210 mg kavalactones) daily for 8 weeks
Outcomes	HAM-A total score. Mean difference, 95% confidence interval 17.9; 9.0 to 26.9
Notes	Adverse events (kava group): restlessness, stomach complaints, drowsiness, tremor Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bhate 1992	duplicate publication
De Leo 2001	conducted in combination with hormone replacement therapy
Lehmann 1989	assessed a single constituent of kava extract
Lehmann 1996	duplicate publication (translated from Kienzler E et al . 1991)
Lindenberg 1990	assessed a single constituent of kava extract

Study	Reason for exclusion
Möller 1989	assessed a single constituent of kava extract
Möller 1992	assessed a single constituent of kava extract
Staedt 1991	assessed a single constituent of kava extract
Warnecke 1986	assessed a combination preparation containing kava extract
Warnecke 1989	assessed a combination preparation containing kava extract

DATA AND ANALYSES

Comparison 1. Kava versus placebo for anxiety

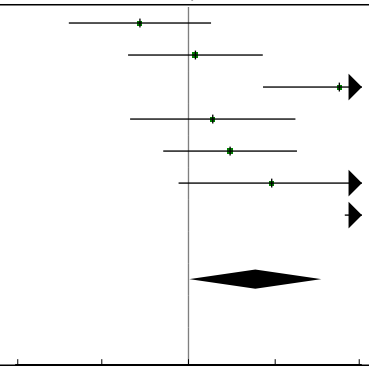
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement (HAMA-score)	7	380	Mean Difference (IV, Random, 95% CI)	3.85 [0.05, 7.66]

Analysis 1.1. Comparison 1 Kava versus placebo for anxiety, Outcome 1 Improvement (HAMA-score).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Connor 2002	17	5.7 (7.6)	18	8.5 (4.2)		15.54%	-2.8[-6.9,1.3]
Geier 2004	25	12.7 (6.7)	25	12.3 (7.3)		15.83%	0.4[-3.48,4.28]
Kinzler 1991	29	12.3 (8.7)	29	3.6 (8.4)		15.12%	8.7[4.3,13.1]
Lehrl 2004	34	10.6 (7.3)	23	9.2 (10)		14.61%	1.4[-3.37,6.17]
Malsch 2001	20	3 (7.5)	20	0.6 (4.6)		15.87%	2.4[-1.46,6.26]
Volz 1997	52	21 (13)	48	16.2 (14.3)		13.76%	4.8[-0.57,10.17]
Warnecke 1991	20	25.6 (12.8)	20	7.7 (15.9)		9.26%	17.96[9.01,26.91]
Total * **	**197**		**183**			**100%**	**3.85[0.05,7.66]**

Heterogeneity: Tau^2=19.89; Chi^2=27.47, df=6(P=0); I^2=78.16%

Test for overall effect: Z=1.98(P=0.05)



FEEDBACK

Comment Safety warns about kava

Summary

We've been alerted to safety concerns about kava products, noting that Swiss and German authorities have withdrawn these from the market after concerns about liver toxicity. The US FDA is also investigating the status of kava. We have added a notice to the Cochrane Consumer Network website, but would like to see this information included in the review as a matter of urgency. We believe that consumers would like to know that some countries believe these products may not be safe.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Please see response to Comment Number 02.

Contributors

Comment Safety warns about kava
Sender Hilda Bastian
Sender Email hilda.bastian@cochraneconsumer.com
Date Received 19/03/02 04:27:00

Comment Update on safety warnings for kava

Summary

New information has surfaced since the message posted on 19/3/02. In addition, one correction is in order for this earlier message.

The US Food and Drug Administration issued a Consumer Advisory on 25/03/2002 (http://www.cfsan.fda.gov/%7Edms/addskava.html) in which it "advises consumers of the potential risk of severe liver injury associated with the use of kava-containing dietary supplements." The agency recommends that "persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, should consult a physician before using kava-containing supplements." The agency also urges both consumers and physicians to report cases of liver or other injuries that may be associated with kava.

The American Herbal Products Association adopted the following labeling recommendation for kava products on 26/03/02: "Caution: Ask a healthcare professional before use if you have or have had liver problems, frequently use alcoholic beverages, or are taking any medication. Stop use and see a doctor if you develop symptoms that may signal liver problems (e.g., unexplained fatigue, abdominal pain, fever, vomiting, dark urine, yellow eyes or skin). Not for use by persons under 18 years of age, or by pregnant or breastfeeding women. Not for use with alcoholic beverages. Excessive use, or use with products that cause drowsiness, may impair your ability to operate a vehicle or heavy equipment."

Hilda Bastien's 19/03/02 message should be corrected to note that German health authorities have not, in fact, withdrawn kava products. Rather, they proposed withdrawal in November, 2001 and requested information to evaluate their proposal. It is my understanding that no final decision has yet been made. Similarly, while some kava products have been removed from the Swiss market, others continue to be sold there.

US FDA was cautious in its communication to refer to any association between kava and the liver as "potential." Nevertheless, the recommendation made by Bastien that consumers be informed of the current concerns that have been expressed by health authorities is sound and is supported by the U.S. herbal trade.

As the President of a trade association that represents manufacturers and marketers of herbal products, including kava products, I have a periferal affiliation with companies that do have a financial interst in this matter. I certify that I have no commercial affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

At the time of writing (August 2002) 68 documented cases of suspected kava hepatotoxicity were on record worldwide. In many of these instances, the exact nature of the extract was not specified. It is clear, however, that all types of extract and synthetic kavain are implicated. In the vast majority of these cases other drugs - some with known hepatotoxicity - were taken concomitantly, a fact, which considerably complicates causal attribution. Similarly, in many of these case reports no data for alcohol consumption or viral infection are provided. The problems typically occurred 2 to 3 months after kava intake; in some cases the length of kava use was not known. The adverse events ranged from mere transient elevations of liver enzymes to severe (often cholestatic) hepatitis and fulminant liver failure. In most instances the patients seemed to have recovered fully after discontinuation of kava. However, 6 patients required liver transplants and 3 patients died. Reliable incidence or prevalence figures are not currently available.

Contributors

Comment Update on safety warnings for kava
Sender Michael McGuffin
Sender Description President, American Herbal Products Association
Sender Email mmcguffin@ahpa.org
Sender Address 8484 Georgia Ave., #370 Silver Spring, MD 20910 USA
Date Received 14/06/02 16:33:23

WHAT'S NEW

Date	Event	Description
27 April 2010	Amended	Contact authors' details amended

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 4, 2001

Date	Event	Description
12 March 2010	Amended	Contact details of contact/first author updated; search dates synchronised
2 November 2008	Amended	Converted to new review format.
20 November 2002	Feedback has been incorporated	Feedback was added, together with a response, on 20 November 2002.
18 November 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Conception and design: MH Pittler, E Ernst
Literature searches: MH Pittler
Analysis and interpretation of the data: MH Pittler, E Ernst
Drafting of the article: MH Pittler, E Ernst
Critical revision of the article for important intellectual content: MH Pittler, E Ernst
Final approval of the article: MH Pittler, E Ernst

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Peninsula Medical School, Universities of Exeter and Plymouth, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Kava; *Phytotherapy; Anxiety [*drug therapy]; Plant Extracts [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans