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SHORT COMMUNICATION

Kava Anxiety Depression Spectrum Study (KADSS): A mixed methods RCT using an aqueous extract of *Piper methysticum*

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Summary
Objectives: To report on the design, significance and potential impacts of the first documented human clinical trial assessing the anxiolytic and thymoleptic efficacy of an aqueous mono-extract of *Piper methysticum* (kava). The significance of the qualitative element of our clinical trial is also explored. The Kava Anxiety Depression Spectrum Study (KADSS) is a 3-week placebo-controlled, double-blind, cross-over trial involving 60 adult participants (18—65) with elevated stable anxiety and varying levels of depressive symptoms.
Aims: The aims of KADSS are: (1) to determine whether an aqueous standardised extract of kava is effective for the treatment of anxiety; (2) to assess the effects of kava on differing levels of depression; and (3) to explore participants' experience of taking kava via qualitative research. The study also provides preliminary assessment of the safety of an aqueous extract of kava in humans.
Conclusion: If results reveal that the aqueous kava preparation exerts significant anxiolytic effects and appears safe, potentially beneficial impacts may occur. Data supporting a safe and effective kava extract may encourage a re-introduction of kava to Europe, UK and Canada. This may provide a major socioeconomic benefit to Pacific Island nations, and to sufferers of anxiety disorders.

Introduction

No substantial advances in pharmaceutical treatments of anxiety disorders have occurred in the last two decades.[1] Orthodox medical treatments of anxiety disorders include synthetic anxiolytics (e.g. benzodiazepines, β-blockers), antidepressants and psychological interventions (e.g. cognitive behavioural therapy).[2] As synthetic pharmacotherapies have significant potential side effects,[1] and in the case of benzodiazepines, present issues of dependence and withdrawal, further research into safe and effective anxiolytics is needed.

Piper methysticum (kava) has good evidence as an effective anxiolytic agent,[3,4] and has demonstrated equivalent

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efficacy to buspirone or opipramol in treating generalised anxiety disorder.[5] Nevertheless, kava was withdrawn from European and UK markets in 2002 due to concerns over reported hepatotoxicity.[6,7] In many of these case reports it was unclear whether kava was responsible for the hepatotoxicity, particularly in those involving concomitant ingestion of other compounds with potential hepatotoxicity (e.g. other medications and/or alcohol).[6] Factors potentially responsible for possible hepatotoxic effects include hepatic insufficiency to metabolise kavalactones, preparations low in glutathione, use of aerial parts or root peelings (higher in alkaloids) in preparations, or the use of acetonic or ethanolic kava extracts.[7–9] As the widespread traditional use of kava beverages in the South Pacific is not typically associated with liver toxicity, it is possible that the method of preparation, plant part used, and kava cultivar, is responsible for any adverse hepatic effects that may have occurred.[10] Research into kava preparations that are reflective of traditional usage is urgently needed. In a World Health Organisation commissioned report assessing the risk of kava products, recommendation 2.1.3 states that ''products from water-based suspensions and further synthetic preparations should be developed and tested in clinical trials and consideration given to using these in preference to acetonic and ethanolic extracts.''[11] To our knowledge, there are no published studies examining the efficacy of a standardised aqueous extract of the peeled root of *Piper methysticum*. As current synthetic pharmacological treatment of anxiety disorders involving benzodiazepines has significant potential health risks and clear dependency issues,[1,12] a standardised aqueous kava extract remains a viable potential therapeutic option.

The potential impact of a successful human clinical trial using an aqueous extract is twofold. Firstly, the impact of European and UK withdrawal of kava was devastating to the South Pacific economies.[10] Evidence of a safe and efficacious non-acetonic/ethanolic extract (aqueous extract) of kava may begin in the process to encourage these governments to re-introduce kava to the markets, thereby benefiting South Pacific economies and enhancing stability in the region. Secondly, as evidence-based pharmacotherapeutic options are currently limited, and present with potentially significant issues of adverse effects and dependence, a safe and effective kava preparation may provide an additional beneficial therapeutic option. It is well established that depressed patients with comorbid anxiety disorders have a poorer prognosis, and exert greater societal demands in terms of increased health care costs and lower work productivity.[2,13,14] A safe and effective aqueous extract of kava may provide significant assistance in reducing the socioeconomic burden of anxiety (with or without co-occurring depression), may improve the quality of life of anxiety sufferers, and potentially benefit the people of the South Pacific.

Design of the trial

To establish efficacy and safety of an aqueous extract of kava, and to explore novel areas of research, we formulated the following trial design. The Kava Anxiety Depression Spectrum Study (KADSS) is a 3-week placebo-controlled, double-blind, cross-over trial. Sixty adult participants (18—65) with elevated stable generalised anxiety and varying levels of depressive symptoms are currently being recruited. Eligible participants undergo a 1-week placebo run-in period before randomisation. Placebo responders will be excluded (i.e. participants obtaining at least a 50% reduction in anxiety scores). Outcomes are measured by the Beck Anxiety Inventory,[15] Hamilton Anxiety Scale,[16] and Montgomery-Asberg Depression Scale.[17] Qualitative semi-structured questionnaires are conducted during the controlled phases at weeks 2 and 3. Five tablets per day of kava (2.66 g each standardised for 50 mg of kavalactones) are prescribed (2 tablets twice a day and one tablet in the evening providing a total of 250 mg kavalactones, the maximum dose approved in Australia). The kavalactone profile of the tablets used in the study should be consistent with the profile of traditional aqueous kava beverages. This will be assessed by an independent analysis of the constituents in the tablets. The kava tablets are supplied by MediHerb Pty Ltd. The use of a 'cross-over design' to our knowledge has not been adopted in any previous kava mono-therapy RCT. While this carries the strength of increasing the statistical power by pooling the data from the participants' individual responses, it also carries the limitation of a possible carry-over effect. Although no 'washout phase' is adopted in the cross-over study, pharmacokinetic clearance of the kavalactones should be complete after approximately 2 days in the kava—placebo group.[18] While there may be an initial carry-over effect, this should be absent by the time of final assessment.

The strengths of using a 'mixed methods' approach in KADSS, is that quantitative outcomes may determine efficacy, while qualitative research will provide an added in-depth, rich examination of the participants experience of taking kava, exploring previously undocumented effects, potential adverse reactions, and any positive therapeutic occurrences. This is important if we are to accommodate and consider outcomes, efficacy and future use/behaviour. While randomised controlled trials remain the gold standard for providing evidence of efficacy for therapeutic interventions, qualitative research provides valuable insight to phenomena that quantitative research and data cannot adequately depict.[19,20] To date we are unaware of any kava RCTs employing a qualitative component.

Aims and predictions of the study

The aims of KADSS are: (1) to determine whether an aqueous standardised extract of kava is effective for the treatment of anxiety; (2) to assess the effects of kava on differing levels of depression; and (3) to explore participants' experience of taking kava via qualitative research. The study also provides assessment of the safety of an aqueous extract of kava in humans. Our prediction is that if the kava preparation exerts a significant anxiolytic effect, the efficacy may be reduced in participants with higher levels of depression. In accordance with our previous study using an aqueous extract of kava (prescribed in a combination with St John's wort),[21] and in vivo results by Singh and Devkota,[22] we expect the extract to be safe. It should however be noted that RCT sample sizes are too small to detect any potential rare occurrence

of hepatotoxicity. Regardless, the 'heterogeneous' sample used in the study is representative of 'real world' use, and this is likely to provide a high external validity of findings, and encourage greater confidence in the product's safety. Furthermore, the recruitment of participants with co-occurring depression and anxiety mirrors the diagnostic norm, as comorbidity is the rule, not the exception.

Conclusion

KADSS will critically examine whether an aqueous extract of kava is effective in the treatment of anxiety, and will provide preliminary assessment of its clinical safety. If the outcome of KADSS reveals a clinically significant anxiolytic effect, the study will advance the case for the re-introduction of kava to the UK and European markets. KADSS will also assess whether the efficacy of kava is altered by depression level. To our knowledge clinical trials of kava using depression outcomes have not been conducted. It is currently not definitively known whether kava has thymoleptic or depressogenic effects, and whether it can be clinically recommended or contraindicated in unipolar or bipolar depression, or in comorbid presentations of depression with other psychiatric disorders. If we can determine this, the results will impact clinical recommendations of kava use (i.e. whether it should be contraindicated or recommended in depressive presentations). Qualitative assessments are expected to identify previously known, and possibly unknown, effects of kava. This appears to be the first documented clinical trial using an aqueous extract of kava in humans; and the first which systematically assesses the efficacy of kava versus placebo in a sample with varying levels of depression.

Conflict of interest statement

Kerry Bone is a consultant to the company MediHerb, the company that supplied the herbal medicine tablets. Kerry Bone contributed advice in the design of the trial; however, he maintained absolute separation from the conduct of the trial.

Funding source

The kava tablets used in the study are supplied by MediHerb Pty Ltd.

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