

KAVA REPORT 2003

IN-DEPTH INVESTIGATION INTO EU MEMBER STATES MARKET RESTRICTIONS ON KAVA PRODUCTS

PART III

Experts Comments on the Decision of the German BfArM

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1. Introduction

Most of the decisions made by national health authorities in Europe and other countries, concerning withdrawal of market authorisation or official warnings on kava preparations, were based on the on the evaluations of efficacy and safety made by the German Federal Institute for Drugs and Medical Devices (BfArM). Therefore, it is worthwhile to take closer look at its official statements and actions as well as at the justification of its measures. This will be done in the following paragraphs.

2. Comments on the evaluations of the BfArM

In its official letter the German BfArM justified the withdrawal of market authorisation of kava preparations with a revised benefit-risk evaluation, after the occurrence of adverse drug reactions resulting in liver damage in 39 cases. In this letter the BfArM wrote that kava intake causes severe adverse effects and that the efficacy of kava in the claimed indication cannot be regarded as approved [5].

We do not agree with the evaluations made by the BfArM. In the following document we will discuss and comment on the conclusions of the BfArM concerning the efficacy, safety and benefit-risk ratio of kava.

2.1. Efficacy of kava preparations

In the justification of the withdrawal of market authorisation the BfArM also wrote that the presented trials couldn't be regarded as a reliable source for a proven efficacy. The BfArM criticised that in the trials, relevant for the benefit-risk-assessment, have not distinguished between different states of anxiety disorders when including patients. Furthermore it criticised the methodological value of the trials. [5].

2.1.1. Comments on the efficacy

We do not agree with this evaluation of the BfArM concerning the efficacy of kava products. When all the available data is evaluated, the efficacy of kava has to be considered as approved.

Apart from the clinical trials (see Expert Report), in which the efficacy of kava was proven, we refer to other experts who confirm our evaluations. One of those is an official commission that was implemented by the German Health Ministry for only one task: to screen for drugs that conform to the criteria for evidence based medicine and to work out a list to include all of these drugs [10].

Kava was listed there. It should include **“all medications that are appropriate for an adequate sufficient and necessary treatment of diseases or major health disorders; precondition for the inclusion in the main part of this list is a more than minor therapeutically benefit, compared to the maximum therapeutical effect achievable”**. Furthermore, the evaluation should consider the **“quality and reliability of scientific data and its therapeutic relevance as well as the prospects of success of the therapeutic measure”**.

1. Evaluation on the efficacy of kava by an independent expert commission implemented by the German Health Ministry

It appears strange that, only 4 month before the BfArM said that there is no proof for the efficacy of kava, **an independent expert commission implemented by the German Health Ministry** came to a very different conclusion than BfArM when they evaluated the available data. This expert commission consisting of 11 specialists in medicine, pharmacology and mathematical statistics, **evaluated the efficacy of kava as approved**. It confirms, that **kava conform to the criteria of evidence based medicine**. Accordingly, kava was included in the German draft positive list for reimbursable drugs [7].

2. Statement of the Expert Commission E implemented by the German Health Ministry

The German expert Commission E, is **another independent expert commission implemented by the German Minister of Health** to advise the BfArM in regulatory affaires concerning herbal drugs. In the Monograph of this Commission (1990) the efficacy of kava was evaluated, as was approved [2].

Recently (2002) the Commission E **reconfirmed their former evaluations** on the efficacy of kava in saying that “the members of the Commission E, re-evaluating the relevant data, **still regard the efficacy of kava as approved** [3].

3. Meta-Analysis performed by Pittler and Ernst

Having critically reviewed 7 randomized, placebo-controlled, double-blind clinical trials the authors concluded, that “the evidence presented here suggest that kava extract is relatively safe and more efficacious than placebo in the symptomatic treatment of anxiety” [8].

2.1.2. Methodological Quality

We do not agree with this evaluation of the methodological quality of the relevant trials, nor do we agree with the criticism of the BfArM concerning the indication.

The indication as carefully worded in the monograph of the German Commission E on kava (1990) and reads as follows: “Condition of nervous anxiety, stress and restlessness”.

We agree with the BfArM that the diagnostic criteria have changed since this time. Various subgroups of anxiety states are now distinguished and may require individual treatment. However, kava has been recommended for mild and moderate anxiety disorders. Its efficacy for the claimed indication was proven in several clinical trials. Several more recent trials have confirmed these results. Therefore, one cannot draw the conclusion that because of a change in diagnostic criteria, this drug has no proven efficacy. It should possibly be reconsidered whether the claimed indication should be made more specific.

1. Meta-Analysis performed by Pittler and Ernst

These authors are acknowledged specialists in the field of methodological evaluations on clinical trials. Furthermore the authors contacted other experts on the subject to provide further information. ***In their systematic review and meta-analysis six of the seven trials scored at least 3 of possible 5 points on a ranking scale assessing methodological quality. Three of the seven trials achieved a score of 5*** [8]. Trials having been published after June 1998 are not included in the systematic review and meta-analysis.

2.2. Safety of kava preparations

In its official letter the German BfArM wrote that the re-evaluation of the benefit-risk-ratio is primary based upon 39 adverse event reports (AERs) affecting the liver and associated with kava products, 3 of which led to death. It further says that about half of these AERs are well documented, whereas the other half cannot be included in the evaluation, since they lack detailed information [5].

2.2.1. Evaluation of case reports

After having reviewed all available information on case reports on hepatotoxic effects of kava preparations ***we do not agree with the evaluations made by the BfArM.*** We further had to realise ***that the BfArM has obviously not carefully reviewed the case reports and misinterpreted available data.***

However we critically evaluated all of the 76 case reports worldwide. The electronic database, which served as a basis for our case analysis is attached as Appendix II in the expert report on the clinical documentation of kava kava.

The case analysis, where our findings are documented in detail, is attached as Appendix I in the expert report on the clinical documentation of kava kava.

Here is a brief summary of our findings:

- 14 of these cases obviously cannot be related to the intake of kava.
- In 22 cases a potentially concomitant treatment was identified.
- In 6 cases the causality to kava is considerably doubtful
- In 30 cases the available data is too fragmentary for an assessment
- Only in the 4 four remaining cases there is a probability of causal relationship to the intake of kava containing products

In 3 of these 4 cases, kava was taken at dosages two to three times as high as is recommended by the German Commission E, and exceeded the recommended period of treatment (see Expert Report, Appendix I).

Several other renowned experts in the field of pharmacology and toxicology analyzed the adverse event reports (AERs) associated with kava products conform to our evaluations, and all came to the same result:

- Many of the AERs associated with kava consumption lack important details and clearly do not represent a sound scientific basis for justifying the ban of kava as done by the German Federal Drug Agency (BfArM).
- Kava taken at the appropriate dosage by persons not concurrently taking drugs associated with liver damage, without excessive alcohol consumption or pre-existing liver disease or hepatitis with compromised liver function, represents a safe and effective phyto-medicine against anxiety and stress disorders.

Among others, the following scientific experts, in addition to Dr. Gruenwald, confirm the safety of kava.

1. *Analysis of case reports by Dr. Donald Waller, toxicologist of the University of Illinois at Chicago, USA*

In November 2001 Dr. Waller was requested by AHAP (American Herbal Products Association) to evaluate all known reports of adverse events related to kava. In this report he analyzed 26 cases reported to the FDA and about 30 cases collected by European authorities. In summary, Dr. Waller concluded that, **“based on currently available information, that kava when taken in appropriate doses for reasonable periods of time has no scientifically established potential for causing liver disease”**. In his opinion **“...there is no clear evidence that the liver damage reported in the U.S. and Europe was caused by the consumption of kava”**.

As with every pharmacological active agent, there is always the risk of side effects and in relation to kava he warned that the concomitant intake of drugs associated with liver damage, excessive alcohol consumption and pre-existing liver disease are conditions, which may preclude any kava intake.

He also criticized that “these reports are seriously lacking details...little can be concluded about most of these cases.” He wrote that ***the classification of causality of the cases made by BfArM “is largely incomprehensible and arbitrary”*** [12].

Dr. Waller’s report was provided to FDA in February 2002. The consumer advisory of FDA issued, contained almost the same messages included in this report.

2. Analysis of case reports by Dr. M. Schmidt and Prof. A. Nahrstedt, pharmacologist, University of Muenster, Germany (February 2002)

This analysis states that regarding the currently discussed hepatotoxic side effects a superficial analysis of the available data by the BfArM generated a distorted picture of the actual risk to the liver from kava extracts.

In its release of reports to the media, ***the BfArM left out significant portions of the case information.*** The one and only reported death is now known to be due to an alcoholic liver failure in an elderly woman who also happened to be taking Kava at the same time. Four cases were listed twice; 3 had no connection with Kava; 11 had probable causal connection to other prescription medication; 4 had an uncertain causal connection to Kava, but could not be excluded; in 6 others the causal connection with Kava could not be determined; in 3 the cause was listed likely due to the excessive dosage and misuse of Kava; and in only 1 where Kava was taken within the recommended dosage range was it listed as the likely cause of liver toxicity. ***Therefore the withdrawal of market authorization for medicinal kava products was completely unjustified*** [9].

3. Review of Dr. A. Denham and co-workers, University of Central Lancashire, UK (J. Alternat. Complement. Med., 8, 2002)

This review of BfArM case reports was prepared on behalf of the Traditional Medicines Evaluation Committee, a subcommittee of the European Herbal Practitioners Association. It was submitted to the U.K. medicines Control Agency and Committee of Safety of Medicines in January 2002. According to the other pharmacological experts the report states that ***most of the adverse events cited by BfArM should not be attributed to kava*** [4].

4. Statement of the German pharmaceutical trade associations (BAH and BPI), January 2002

In addition, most of the reported cases, the causality between kava intake and liver reactions is not clear because further medication was used which might have caused liver toxicity. ***In many cases, detailed information on the patients' history, co-medication, consumption of alcohol and further particulars are missing, thus not permitting a sound evaluation of these cases*** [1].

2.2.2. General safety

Kava has to be regarded as a safe drug. Adverse effects reported in clinical trials including about 10 000 patients were rare and mild.

1. Statement of German Commission E

The scientists of the Commission E commented the safety evaluations as follows:

“The members of Commission E ***do not share BfArM's opinion about the risk under correct and stipulated use of the medicinal product...***” [3].

2. Review by Dr. C. Stevinson, Dr. A. Huntley and Dr. E. Ernst, Department of Complementary Medicine, University of Exeter, UK (Drug and Safety, 25, 2002)

In the recent publication the researchers concluded that “data from short-term post-marketing surveillance studies and clinical trials suggest that ***adverse events are, in general, rare, mild and reversible...***It is concluded that when taken as short-term mono-therapy at recommended doses, ***kava extracts appear to be well tolerated by most users***” [11].

3. Statement of Dr. P.A. Cox, botanist, director of the National Tropical Botanical Garden, Hawaii

During his extensive ethnobotanical studies in Pacific island group where the drug kava is used regularly, Cox stated that he has seen no evidence of liver problems. “The indigenous people of the Pacific have used kava longer than anyone in Europe, and if there is a liver threat, they should be suffering from it.” Although Kava has been found to be associated with a few mild side effects, such as a skin rash, when taken at high doses for prolonged periods of time, it has never been found to cause hepatotoxicity. Dr. Paul Cox stated, ***“in my nearly three decades of work in Polynesia, I have never heard of a single case of liver toxicity caused by kava consumption.”***

2.3. Benefit-Risk-Ratio

The German BfArM considers the ratio of potential benefit and risks related to the intake of kava preparations including homoeopathic preparations up to D4 as unfavourable. The BfArM states that the occurrence of hepatotoxic adverse effects, related to the intake of kava, constitute a considerable health risk that is not compensated by an approved therapeutic effect in the claimed indication and for the dosages used [5].

Taking into account the comments stated in the paragraphs 2.1. (Efficacy) and 2.2. (Safety) it seems at least questionable how the evaluations of the BfArM led them to this benefit-risk-ratio. Having evaluated all the published data and statements **we cannot agree with the BfArM's benefit-risk-ratio**. Our result of the benefit-risk-assessment are confirmed by several experts and health authorities, amongst them the Food and Drug Administration (FDA), German commission E, the German pharmaceutical trade associations Bundesverband der Arzneimittelhersteller (BAH) und der Bundesverband der Pharmazeutischen Industrie (BPI).

1. FDA notice on June 27, 2002

FDA published the following notice: "FDA has no current intentions to seek a recall or other regulatory action but would rather continue to approach kava from a science-driven perspective. This means a continued study of the AERs and continued discussion with industry...FDA is initiating in vitro studies to better understand metabolism of key kava components and possible relationship of the AERs." This attitude has not changed in the recently published report (November 29, 2002) of the U.S. Center of Disease Control evaluating the European and American AERs. FDA advised consumers and health-care providers about the potential risk for hepatic toxicity with the use of kava-containing products, but these products can still be marketed legally [6].

2. Statement of German Commission E

In contrast to BfArM, the members of the German Commission E are convinced of the presented scientific data on the efficacy of Kava and **consider the risk-benefit ratio and the therapeutic benefit for the patient positive...and ...are of the opinion that there was no imminent danger justifying the measure taken** [3].

3. Statement of the German pharmaceutical trade associations (BAH and BPI), January 2002

The industry's statement concludes that **the presented data** on the benefit/risk assessment of kava-containing medicines **do not justify the withdrawal of marketing authorizations** [1].

3. Comments on the actions of the German BfArM

3.1. Reaction on the revised benefit-risk-ratio of the SWISSMEDIC (former IKS)

In September 2000 the government notified kava marketers of safety concerns regarding kava, based on the initial four case reports. In 2001 the authorities concluded a drug safety protocol. All cases except one were related to an acetone kava extract (Laitan, manufactured by the German company Schwabe), which was therefore provisionally suspended and definitely withdrawn in April 2001.

The German BfArM, at this time, did not see a need for a revised benefit-risk-assessment in Germany. Although the products differed from the ones available in Germany, it is questionable that the BfArM at this time did not even think about a new evaluation of kava, and only one year later cancelled the registration of kava containing products.

3.2. Treatment of the German Commission E

The scientists of the Commission E are experts in the field of herbal medicinal products and advise the German Health Authority (BfArM). This commission was exclusively implemented to advise the BfArM on regulatory affairs concerning these products. Before taking measures this commission should be heard by the BfArM and the commission should propose further proceedings. But their scientific competence and their evaluations were ignored. They comment on the withdrawal of Kava-containing medicinal products from the German market by BfArM as follows:

“The members of Commission E are taken aback by the way of acting of BfArM as regards the benefit / risk assessment and the withdrawal of Kava-containing medicinal products. They think that their scientific competence was not taken into consideration and that their function is questioned...and, in contrast to BfArM, are convinced of the presented scientific data on the efficacy of Kava and consider the risk-benefit ratio and the therapeutic benefit for the patient positive...are of the opinion that there was no imminent danger justifying the measure taken [3].

3.3. Withdrawal of market authorisation of kava preparations up a homoeopathic concentration of D4

To underline the questionability of the measures taken by the BfArM, this decision should be mentioned here. With the withdrawal of market authorisation of homoeopathic kava preparations up a concentration of D4 [5] *the German BfArM lists kava among the most poisonous and toxic substances in the world.*

As far as we are concerned this decision cannot be regarded as justified and appropriate. I do not think that we need to cite an expert to confirm this. If this drug is so poisonous and frequently consumed in high quantities by the inhabitants of a number of pacific islands, for 2000 years, this would have been reported.

3.4. Possible alternatives to a withdrawal of market authorisation

We agree with the German BfArM, that it was correct to react to the severe AERs. However, there is a catalogue of possible measures that can be taken before the withdrawal of market authorisation. The options available include revising the drug safety protocol or change the regulatory status from OTC to prescription drug. Regarding the efficacy, safety and the benefit-risk-ratio, it does not appear to be logical that the German BfArM chose the gravest measure available. Especially when the therapeutic alternatives and their potential risks and their unsatisfactory patient compliance is taken into account. The Food and Drug Administration showed that there were alternatives to a withdrawal of market authorisation. And the German Commission E gave recommendations to guarantee the safe use kava preparations.

1. The U.S. Food and Drug Administration (FDA)

The U.S. Food and Drug Administration (FDA) demonstrated that there are other options available. This health authority reacted in a much more appropriate manner and advised consumers and health-care providers about the potential risk for hepatic toxicity with the use of kava-containing products. FDA stated ***that it has no current intention to seek a recall or other regulatory action but would rather continue to approach kava from a science-driven perspective.*** It should not be assumed that the FDA would risk the health of patients if kava intake was associated with imminent danger.

2. Recommendations of the German Commission E

Due to the occurrence of severe AERs the members of Commission E drafted recommendations for the correct and stipulated use of *medicinal* kava preparations [3]. These recommendations were:

1. Medical prescription for Kava-containing medicaments.
2. Clear indication: Slight until moderate generalized anxiousness. Depression is not an indication.
3. Maximum daily dosage corresponding to 120 mg kavapyrones.
4. Package size for 120 mg kavapyrones maximum 30 units.
5. Usual duration of therapy: 1 month, maximum 2 months.

6. Determination of liver values (GPT and gamma-GT) before treatment and then once a week.
7. Optional: Determination of liver values at the end of treatment (important for a possible later treatment).
8. Avoiding concurrent medication with potentially hepatotoxic medicaments, especially beta-blockers, antidepressants and anti-migraine preparations. Be cautious with alcohol.

The expert agrees with these recommendations and considers them to be appropriate measures to secure the use of kava preparations.

4. Conclusions

In conclusion, the expert states that the BfArM's evaluations of the efficacy and safety of kava preparations do not reflect the scientific data available for this drug. The efficacy of kava is clearly proven and has been confirmed by most experts in the field of pharmacology and medicine and by an expert commission. Furthermore, all experts, who have critically reviewed the case reports of hepatotoxic effects due to the intake of kava, criticized the BfArM for having drawn its conclusions on fragmentary data and stated that the classification of causality of the cases made by BfArM "is largely incomprehensible and arbitrary". All experts agree that on the basis of the available data, apart from one possible exception, none of the cases reported can be related to the intake of kava preparations.

Taking this into consideration, the measures taken by the BfArM do not appear to be appropriate. There were several other options open for the BfArM to react to the occurrence of adverse effects, as shown by the U.S. Food and Drug Administration (FDA). Furthermore, it must be mentioned that the BfArM did not consider the advice of the German Commission E, which was implemented by the German Health Ministry to advise the BfArM on such issues.

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