Kava-kava Extract WS 1490 versus Placebo in Anxiety Disorders – A Randomized Placebo-controlled 25-week Outpatient Trial

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101 outpatients suffering from anxiety of non-psychotic origin (DSM-III-R criteria: agoraphobia, specific phobia, generalized anxiety disorder, and adjustment disorder with anxiety) were included in a 25-week multicenter randomized placebo-controlled double-blind trial with WS 1490, a special extract of kava-kava. In the main outcome criterion, the Hamilton Anxiety Scale (HAMA), there was a significant superiority of the test drug starting from week 8 on. WS 1490 was also found to be superior with respect to the secondary outcome variables. HAMA subscores somatic and psychic anxiety, Clinical Global Impression, Self-Report Symptom Inventory – 90 Items revised, and Adjective Mood Scale. Adverse events were rare and distributed evenly in both groups. These results support WS 1490 as a treatment alternative to tricyclic antidepressants and benzodiazepines in anxiety disorders, with proven long-term efficacy and none of the tolerance problems associated with tricyclics and benzodiazepines.

Introduction

Phytomedical drugs are – at least in Germany – of growing interest. In 1994 they accounted for 10% of the total German pharmaceutical market, in monetary terms about three billion dollars (*Grünwald* and *Büttel*, 1996). Psychoactive drugs derived from plant material are among the most commonly prescribed compounds in the sector: they include ginkgo extract as an antidementia drug and hypericum extract as an antidepressant: Kava-kava is the only substance in this class for the treatment of anxiety.

When in the 18 th century Europeans discovered the South Sea islands, they observed the native inhabitants drinking kava. The Polynesians prepared an extract (cold macerate) from the root of the kava and diluted it with water or coconut milk. This potion was calming and relaxing without producing cognitive disturbances. Ethnomedical reports soon led to searches for the psychoactive compound of the extract, but it was not until 1966 that the German pharmacologist *H. J. Meyer* was able to show that the so-called kava-pyrones were responsible for its psychotropic properties. Their chemical structure, a 4-methoxy-pyron-2 core with variable substituents at the C-6 position, was already known. These kava-pyrones are only poorly soluble in water, which may explain why it has taken so long to prove their efficacy in clinical practice. In plant-derived pharmaceuticals – usually extracts – both the quality of the basic material and the extraction method used are of great importance. Depending on these factors, differently composed extracts may be obtained with consequently different amounts of active agent. A key quality parameter for plant-derived medicines is, therefore, the accurate standardization of the extract to a defined quantity of a particular marker or activity-determining compounds, if these are known (*Reichling*, 1995; *Ihrig* and *Blume*, 1992).

The measure of quality for kava extracts is their pyrone content. In this study a special extract with a high kava-pyrone content, equal to 70% (kava extract WS 1490), was used. This extract has little in common with the original Polynesian kava drink originally made for ceremonial occasions.

Using specific enrichment processes, the kava-pyrone content of the extract is increased approximately tenfold compared to that in kava-kava root. In addition, a number of less desirable components such as tannins are eliminated during the extraction process. In human pharmacology studies, this kava extract exhibited a tendency for cognitive improvement, while oxazepam reduced cognitive functions, in several standardized test batteries (*Heinze* et al., 1994; *Münte* et al., 1993) such as reaction time, mental alertness, and rate of recognition.

Two placebo-controlled trials using this extract have been published to date. One (*Kinzler* et al., 1991) compared kava-kava and placebo in a controlled trial on 58 outpatients suffering from anxiety, tension, and agitation syndromes of nonpsychotic origin and found a significant superiority of the verum group after a treatment period of four weeks. No difference in tolerability occurred. In a second, eight-week placebo-controlled trial (*Warnecke*, 1991), a total of 40 outpatients were treated either with kava extract or placebo. The patients, all women, suffered from climacteric psychosomatic disturbances. Again, a significant treatment advantage of kava-kava became apparent. In a comparative trial (*Woelk*, 1993) kava-kava was compared for six weeks with oxazepam (daily dose 15 mg) and bromazepan (9 mg) in outpatients fulfilling the same inclusion criterion as cited under the first trial reported. No significantly different treatment effects were observed, all three compounds showed the same

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anxiolytic potency as measured by the HAMA. A shortcoming of all these trials is the lack of operationalized diagnoses as inclusion criteria (for a critical review, see *Volz* and *Hänsel*, 1994).

Thus, there is a small but growing body of evidence that kava-kava may possess some anxiolytic effects. The major shortcomings of the trials mentioned above clearly are that (i) the treatment periods were rather short, and (ii) the number of patients included was only small.

In order to avoid these pitfalls, we performed a long-term controlled randomized efficacy and safety trial (25 weeks) comparing kava-kava with placebo. The patients included were diagnosed according to DSM-III-R (APA, 1987) to obtain well-defined categories of psychiatric disorder within the spectrum of anxiety.

Method

The study was conducted in a multicenter randomized placebo-controlled double-blind design. The active compound was WS 1490, a lipophilic extract of kava-kava rhizome containing 90 – 110 mg dry extract (= 70 mg kava-lactones) per capsule[1]. One capsule (either kava extract or placebo) was administered three times a day. Ten centers participated in the study, all were general practices with large patient populations in the southern part of Germany. Included were 101 outpatients suffering from anxiety and tension of non-psychotic origin. Patients had to fulfill one of the following DSM-III-R diagnostic criteria: agoraphobia (DSM-III-R: 300.22), specific phobia (300.29), social phobia (300.23), generalized anxiety disorder (300.02), and adjustment disorder with anxiety (309.24). In the Mehrfachwahl-Wortschatz-Test (multiple-choice vocabulary test), version B (MWT-B, *Lehrl*, 1978), a maximum of 13 mistakes were allowed. On the Hamilton Anxiety Scale (HAMA, *Hamilton*, 1959) a score of at least 19 was required. The protocol was approved by an Ethical Review Board, and written informed consent was obtained. The trial was conducted according to good clinical practice guidelines, including source data audit. Major exclusion criteria were comedication with psychoactive compounds, hypotension (blood pressure lower than 90/60 mmHg), cerebellar ataxia, sleep apnea syndrome, a history or presence of substance abuse, clinically relevant cardiovascular, renal, hepatic, or respiratory diseases, and malignancies. Patients with an increase or decrease of more than six points on the HAMA at the end of the one-week single-blind placebo washout period preceding the trial were also excluded.

Trial duration was 25 weeks after a one-week single-blind placebo washout period. After a 24-week random treatment period, a one week placebo washout was performed.

The following ratings were performed at the beginning of the placebo washout period and at weeks 0, 12, and 24: HAMA (main outcome criterion), self-report symptom inventory 90 items – revised (SCL-90-R, *Derogatis* et al., 1973), Clinical Global Impression (CGI, NIMH, 1970), Adjective Mood Scale (Bf-S, *von Zerssen*, 1986), and registration of adverse events according to an open, non-leading questionnaire. Additional HAMA ratings and adverse event (AE) checks were performed at weeks 4, 8, 16, and 20. Blood tests were carried out regularly. After the final one-week placebo washout period, all efficacy and safety tests were repeated.

The main efficacy analysis was based on an intent-to-treat approach. Additional analyses included all patients not violating protocol (per-protocol approach) and descriptive analyses of the additional efficacy and safety parameters. The main target parameter HAMA was tested using the U-test stratified for center (level of significance: $a = 0.05$). An a priori sample size calculation was performed based on a power of 90% and a stochastic superiority of the verum group of at least 0.67 (*Noether*, 1987).

Results

Efficacy

101 patients (52 on WS 1490, 49 on placebo) were included in ten centers. For the intent-to-treat approach 100, for the per-protocol approach 73, patients were eligible. The main demographic variables are presented in Table **1**. Most patients suffered from more than one anxiety diagnosis, so the degree of comorbidity was pronounced. This is in accordance with recent literature (*Bronisch*, 1996). Relevant concomitant diseases were (no. of patients in placebo versus verum groups): hypertension 11 vs. 9, hyperlipidemia 4 vs. 6, gonarthrosis 5 vs. 5, diabetes mellitus 6 vs. 3, cardiovascular diseases 6 vs. 3.

Table 1 Main demographic data of patients. No. of patients or mean (SD); p-values refer to the two-sided chi-square test (sex) or U-test (age, HAMA score)

	WS 1490	Placebo	p-value
Sex (male/female)	15/37	12/36	0.62
Mean age in years (SD)	54.1 (17.1)	53.7 (15.5)	0.94
Mean HAMA score at week 0 (SD)	30.7 (7.2)	31.4 (9.2)	0.98

The HAMA total score showed a pronounced decrease in both groups. It decreased in the WS 1490 group from a mean of 30.7 (SD 7.2) at week 0 to 13.4 (9.6) at week 12 and 9.7 (9.9) at week 24. The corresponding results in the placebo group were 31.4 (9.2) at week 0 and 18.0 (9.1) and 15.2 (9.6) at week 12 and 24, respectively. The WS 1490 group was superior at all monitorings during the treatment phase (Table **2** and Fig. **1**). The difference was statistically significant at week 8 ($p = 0.02$, U-test, two-sided) and increased later in the treatment period (week 12: $p = 0.002$, weeks 16, 20, 24: $p < 0.001$, U-test, two-sided). The per-protocol analysis showed a very similar result.

The HAMA subscores "somatic anxiety" comprising items 7 (somatic [muscular]), 8 (somatic [sensory]), 9 (cardiovascular symptoms), 10 (respiratory symptoms), 11 (gastrointestinal symptoms), 12 (urogenital symptoms) and 13 (autonomic symptoms) and the subscore "psychic anxiety" with the items

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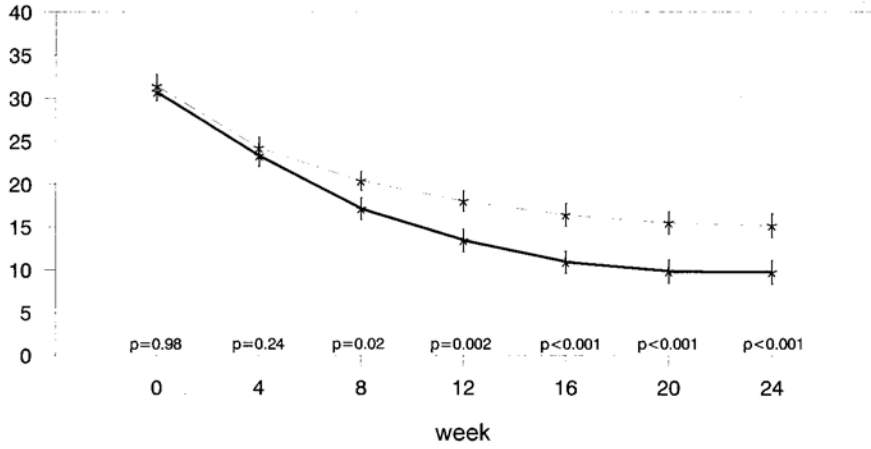

Fig. 1 HAMA total score (mean ± SEM) during the 24-week treatment period. p-values refer to the two-sided U-test stratified by center.
(dashed line: placebo, solid line: WS 1490)

1 (anxious mood), 2 (tension), 3 (fears), 4 (insomnia), 5 (intellectual), 6 (depressesd mood), and 14 (behavior at interview) were analyzed descriptively, and showed a statistically significant advantage for the verum starting at week 8. Somatic anxiety was reduced under WS 1490 from a mean of 1.9 to 0.6 (placebo 1.7 to 1.0, p = 0.02, U-test, two-sided), and mental anxiety from 2.4 to 0.6 (placebo 2.4 to 1.3, p = 0.02).

The CGI (Table **2b**) showed also a very clear-cut result. After 12 weeks of treatment, 20.0% of the patients treated with WS 1490 were rated as "very much improved" in their psychopathological state, compared to 10.5% in the placebo group, after 24 weeks of treatment the corresponding rates were 53.1% versus 30.2%. If we combine the categories "very much improved" and "much improved" and the categories "slightly improved", "no change", and "slightly worse", a statistically significant advantage for those patients treated with WS 1490 emerges: after 12 weeks of treatment almost twice as many verum as placebo patients were rated at least much improved (69.2% versus 37.2%, p = 0.001; chi-square test, two-sided); the result after 24 weeks of therapy was also impressive (75.5% versus 51.2%, p = 0.015, chi-square test, two-sided).

The results are very similar for the self-rating scales (Table **2a**). In the SCL-80-R, WS 1490 showed a statistically significant superior efficacy from week 12 on (p< 0.05, U-test, two-sided); in the case of the Bf-S, the result was borderline significant at week 24 (p = 0.08, U-test, two-sided).

General practitioners with a large outpatient population were chosen as investigators in order to cover the typical situation in practice. This led to a considerable variability of demographic data and baseline values between collaborating centers, which explains center differences with respect to the HAMA total score (p< 0.001, two-factor ANOVA, two-sided).

Tolerance

During the study period, six AEs in five patients were reported in the verum group. Four of these six AEs were rated by the investigator as not being related to the compound under

week	HAMA-total score WS 1490	Placebo	p	SCL-90-R (GSI) WS 1490	Placebo	p	BF-S-total score WS 1490	Placebo	p
0	30.7 (7.2)	31.4 (9.2)	.98	1.7 (0.6)	1.7 (0.6)	1.00	39.6 (11.0)	40.0 (12.5)	.46
4	23.3 (9.2)	24.2 (8.6)	.23						
8	17.1 (9.1)	20.3 (7.6)	.02						
12	13.4 (9.6)	18.0 (9.1)	.002	1.0 (0.6)	1.3 (0.6)	0.01	20.5 (15.4)	29.2 (15.4)	.01
16	10.9 (9.1)	16.4 (9.1)	<.001						
20	9.8 (9.8)	15.5 (9.1)	<.001						
24	9.7 (9.9)	15.2 (9.6)	<.001	0.7 (0.6)	1.0 (0.6)	.04	16.3 (13.8)	27.5 (15.5)	.08

* The GSI is defined as the sum of the answers to all items divided by the total sum of the items (90).

Table 2a Main efficacy results. HAMA, SCL-90-R (GSI*), and Bf-S. Mean (SD); p-values refer to the two-sided U-test

	WS 1490	Placebo	WS 1490	Placebo
very much improved	26 (53.1)	13 (30.2)		
much improved	11 (22.4)	9 (20.9)	37 (75.5)	22 (51.2)
slightly improved	8 (16.3)	17 (39.5)		
no change	4 (8.2)	3 (6.1)	12 (24.5)	21 (48.8)
slightly worse	0	1 (2.3)		
	p = 0.020 (U-test, two-sided)		p = 0.015 (chi-square test, two-sided)	

Table 2b Main efficacy results. CGI, item 2, week 24. no. of patients (%)

investigation, two (in both cases "stomach upset") were rated as "possibly related". Fifteen AEs from nine patients were reported in the placebo group, two ("vertigo and palpitation", "vertigo") were rated as "possibly related", one ("vertigo") was judged to be "related". Thus, the overall tolerability of WS 1490 was excellent. Regarding laboratory results (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, creatinine, urine hydrogen ion concentration, proteins, glucose, nitrite, and ketone) no clinically relevant changes were noted in either group.

Mean blood pressure at week 0 was 134.9 (SD: 15.9)/80.9 (7.0) mmHg in the WS 1490 group, 136.1 (13.2)/81.0 (7.9) in the placebo group. At week 24 the respective figures were 133.5 (14.6)/80.5 (7.8) and 135.7 (12.2)/80.1 (7.6). A heart rate of 77.4 (8.5) was recorded at week 0 and of 76.2 (7.6) at week 24 in the verum group; in the placebo group, the respective figures were 76.3 (8.0) and 76.8 (6.6).

The analysis of dropouts is presented in Table **3**, which shows that seven patients dropped out under placebo and only three under verum, two of them reporting an improvement as a reason for dropout. Overall, the dropout rate was about 10%, with reasons for dropout that are quite common for placebo-controlled trials in anxiety disorders.

Table 3 Dropouts during the study

Patient Number	Reason for dropout	last evaluation
WS 1490		
107	improvement of symptoms	week 20
707	insufficient compliance	week 12
708	improvement of symptoms	week 12
placebo		
105	worsening of symptoms	week 8
110	insufficient compliance	week 8
502	at patient's request	week 8
703	reasons unknown	week 8
706	moved to a different area	week 12
1007	insufficient compliance	day 1

Discussion

To our knowledge, this is the first long-term placebo-controlled trial investigating safety and efficacy of a kava extract in anxiety patients. Three major conclusions can be drawn.

(i) The short-term efficacy of WS 1490 is superior to that of placebo. As can be seen from the main efficacy parameter (HAMA total score) and from the other efficacy instruments used (HAMA subscores "psychic anxiety" and "somatic anxiety", CGI, SCL-90-R), WS 1490 was superior to placebo after eight weeks of treatment. The patients included suffered from a moderate to severe anxiety syndrome, as is obvious from a mean initial total score on the HAMA of about 30. The scores of both subsyndromes "psychic" and "somatic" anxiety were reduced by a comparable degree. Since all efficacy instruments (observer and self-rating scales) showed the same trend, this result seems to be robust.

(ii) The long-term efficacy of WS 1490 is superior to that of placebo. Again, this superiority became obvious in all efficacy instruments used. The initial improvement of the first eight weeks (reduction of the HAMA score from 30 to 17) continued for another 16 weeks, culminating in a total reduction of the HAMA score from 30 to 9. This means that long-term treatment shows even greater efficacy than short-term treatment.

(iii) The tolerance of the compound is good. Adverse events were rarely reported in either group. The AE "stomach upset" judged by the investigators to be "possibly related" to the test compound was noted twice. Since this is also a typical anxiety symptom, no definite interpretation seems possible. Laboratory values, blood pressure, and heart rate did not show any systematic change during the treatment period. More patients dropped out under placebo, which demonstrates good tolerance of the verum, and is also an additional indication of the good efficacy of the kava extract.

These overall good results must be discussed in respect of the two other standard pharmacotherapeutic strategies for treating anxiety disorders, i.e. benzodiazepines and tricyclic antidepressants. As to benzodiazepines, their effectiveness in this indication is beyond any doubt, and the short latency needed to establish the desired anxiolytic effect is a particular advantage. The two major drawbacks of this class of compounds are their dependency potential and their side-effect profile. Especially when administered on a long-term basis, benzodiazepines are difficult to withdraw, so that only short-term treatment with the lowest possible dose is advised in physicians' desk references. In this regard, kava-kava is non-problematic. Withdrawal symptoms or dependency developments are not known. Also, in our trial, no withdrawal symptoms occurred in the last trial phase (week 25). The side-effect profile of benzodiazepines, with drowsiness as the predominant symptom, leads to restrictions in driving vehicles or operating machinery. For kava-kava, the results of phase I trials are available and show no detrimental influence of this compound on various psychometric parameters (*Herberg*, 1991, 1993).

Tricyclic antidepressants, also widely used to treat anxiety disorders, have two major side-effects limiting their use: anticholinergic effects, especially for higher doses, which account for a decreased compliance, and direct cardiotoxic effects which make it impossible to administer them to patients suffering from severe cardiac conduction disturbances. Such side-effects are not known with respect to kava.

It seems of special interest that for anxiety disorders hardly any long-term efficacy data based on placebo-controlled trials are available for benzodiazepines or antidepressants. For generalized anxiety disorders, for example, the longest trial with diazepam had a duration of 8 weeks (for a review, see *Volz* et al., 1994). So the present trial represents an effort to establish the very much needed long-term efficacy data for the treatment of anxiety disorders. This seems of importance in view of the chronic nature of these disorders, exemplified by the pronounced anxiety ratings of the placebo-treated patients in our trial at the end of the study.

Our trial had several limitations. First of all, a heterogeneous patient-group was investigated. Most patients had double or

triple diagnoses, mostly including phobia and generalized anxiety disorder. Therefore, no differential effect of the verum regarding a particular diagnosis of the anxiety disorder spectrum could be pinpointed, and only a reduction of overall anxiety occurring in all these conditions could be demonstrated.

Secondly, the verum was superior to placebo only from week 8 on. Two explanations suggest themselves: (i) The placebo response rate was pronounced. In the kava group the HAMA total score dropped from 30.7 to 23.3 in week 4, the respective figures for the placebo group were 31.4 and 24.4. In the trial conducted by *Kinzler* et al. (1991), a less pronounced anxiety score at the start of treatment (25.3 [verum], 24.3 [placebo] and a drop to 12.6 versus 21.0 rendered the difference already statistically significant after four weeks' treatment duration. In other words, our placebo response rate up to week 4 was 22% as compared to *Kinzler's* astonishingly low rate of 13.6%. (ii) The mean duration of the anxiety disorders in our group was 6.5 months. This indicates a chronic state of illness, which would be more treatment-refractory than newly manifested anxiety syndromes. In the *Kinzler* et al. study (1991), no statement about the pretrial duration of the disorder is given.

Thirdly there was a certain depressive comorbidity in our study population, shown by analysis of the HAMA item 6 ("depressed mood"). In the verum group, this item reached a mean (SD) level of 2.53 (0.91) at the beginning of the trial. In the placebo group 2.38 (1.05) was noted. It dropped to values of 0.65 (0.83) (verum) and 1.11 (1.02) (placebo) at week 24, which constituted a statistically significant difference between the two groups ($p = 0.02$, U-test, two-sided). However, the HAMA item 1 ("anxious mood") was more pronounced at the beginning of the study (2.94 [0.85] and 3.08 [0.83]) and the level of statistical significance differentiating the two groups was higher at week 24 ($p = 0.01$, U-test, two-sided) than where HAMA item 6 was concerned. The analysis of these single items leads us to conclude that, first, although a certain depressive comorbidity was present, anxiety was indeed the leading symptom, and, second, that WS 1490 is primarily effective against anxiety.

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