ORIGINAL INVESTIGATION

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Efficacy of kava-kava in the treatment of non-psychotic anxiety, following pretreatment with benzodiazepines

Abstract A 5-week randomized, placebo-controlled, double-blind study was carried out to investigate the efficacy of kava-kava special extract WS®1490 in non-psychotic nervous anxiety, tension and restlessness states. During the first treatment week, the study dose drug was increased from 50 mg to 300 mg per day and pretreatment with benzodiazepines was tapered off over 2 weeks. These dosage adjustments were followed by 3 weeks of monotherapy with WS®1490 or placebo. Outcome measures were the differences between baseline and end of treatment on the Hamilton Anxiety Scale (HAMA) and on a subjective well-being scale (Bf-S), as well as the benzodiazepine withdrawal symptoms. Changes in the Erlanger Anxiety, Tension and Aggression Scale (EAAS) and Clinical Global Impressions (CGI) were analyzed as secondary measures. Treatment safety was checked by interviews, adverse event reports and laboratory investigations. Forty patients (2×20) were included into the study. WS®1490 was superior to placebo regarding the HAMA ($P=0.01$) and Bf-S ($P=0.002$) total scores and all secondary efficacy measures. The tolerance of WS®1490 was not inferior to placebo. The study confirms the anxiolytic efficacy and good tolerance of WS®1490 and shows that a further symptom reduction is possible after a change-over from benzodiazepine treatment.

Keywords Anxiety state · *Piper methysticum* · Anxiolytic agent · Phytopharmaceutical · Kava-kava extract WS®1490 · Randomized clinical trial

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Introduction

During their lifetime, approximately 5% of women and 2% of men suffer from anxiety disorder (pathologically exaggerated anxiety states) at least once. On the South Sea islands, the kava plant (*Piper methysticum*) has been cultivated and consumed for hundreds of years because of its remarkable property to cause anxiety relief and relaxation without adversely affecting mental alertness. All parts of the plant, also known as "Ava pepper" (due to its spicy and slightly bitter flavor) can be used. The fresh or dried parts are pulverized mechanically and then usually mixed with water to produce a drink with anxiolytic and soporific effects. When taken in large quantities it can cause motor ataxia, but impairment of consciousness has not been reported (Hänsel and Woelk 1994).

The extract tested in this study was the special extract WS®1490 (Laitan 50®; Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany), a monoextract from the dried root of the kava plant. It is standardized to 70% kava-lactones, i.e. kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin and desmethoxiyangonin. Studies suggest that these constituents act via the formatio reticularis: as a muscle relaxant on the striated muscles (Kretzschmar and Teschendorf 1974) and as a spasmolytic agent on the smooth muscles of the digestive tract (Kretzschmar 1969). In addition, sedative, anticonvulsive, toponarcotic and antiarrhythmic properties were also demonstrated (Meyer 1966). In EEG studies and other clinical investigations, WS®1490 displayed the activity profile of an anxiolytic agent (Johnson et al. 1991; Kinzler et al. 1991; Warnecke 1991; Woelk et al. 1993; Volz and Kieser 1997) and improved the quality of sleep without influencing sleep patterns or structure (Emser and Bartylla 1991). Furthermore, a positive influence of WS®1490 on cerebral information processing was demonstrated (Münte et al. 1993) and the drug did not adversely affect reaction times during a suitability for driving test (Herberg 1991, 1992).

Animal studies suggest that the anxiolytic effect of kava-kava may be attributable to a modulation of the se-

rotonin$_{1A}$ receptor activity (Walden et al. 1997), and the herbal extract was also found to exhibit a neuroprotective activity (Backhauss and Kriegelstein 1992). Pharmacological studies also demonstrated that (±)-kavain reduced veratridine-induced increase of glutamate in the brain, a neurotransmitter which is able to induce various neurological disorders (Gleitz et al. 1996; Feger et al. 1998). The drug's relaxing and slightly euphoric actions may be caused by activation of the mesolimbic dopaminergic neurons, whereas changes in the activity of 5-HT neurons could explain its slight sleep-inducing action (Sällström Baum et al. 1998).

In a double-blind, controlled trial, no characteristic differences were found between synthetic D,L-kavain and oxazepam in the treatment of anxiety states (Lindenberg and Pitule-Schödel 1990). Woelk et al. (1993) compared WS®1490 to oxazepam and bromazepam and found the anxiolytic efficacy of the herbal extract to be descriptively equivalent to the two benzodiazepines. However, during long-term treatment, the herbal extract did not cause sedative effects and adverse drug reactions such as addiction, tolerance or withdrawal symptoms (Volz and Kieser 1997) frequently found with benzodiazepines. In the same trial, WS®1490 induced significant improvement of anxiety disorders and depression in comparison to placebo, while reducing symptoms like headache, palpitations, stomach-ache and respiratory disorders simultaneously (Volz and Kieser 1997).

The main objective of this study was to investigate the anxiolytic efficacy of WS®1490 compared to placebo over a treatment period of 36 days, in patients previously treated with benzodiazepines, in order to assess the potential of the herbal extract in benzodiazepine replacement therapy. Furthermore, the extract's ability to reduce benzodiazepine withdrawal symptoms was assessed.

Materials and methods

Study population

The trial was conducted at the Ochsenzoll General Hospital, Hamburg, Germany, with a planned sample size of 2×20 trial participants. Eligible patients had to suffer from nervous anxiety, tension and restlessness of non-psychotic origin, resulting in impairment of their performance at work, normal social activities and relationships (diagnosis of agoraphobia (300.22), simple (300.29) or social phobia (300.23), generalized anxiety disorders (300.02) or adaptation disturbances (309.24) according to DSM-III-R. A minimum history of 14 days of uninterrupted treatment with benzodiazepines (lorazepam, bromazepam, alprazolam or oxazepam) was required prior to study inclusion. A medical indication for the discontinuation of the benzodiazepine treatment (e.g. to avoid the benzodiazepines' addictive potential and sedative effects) and the change to an alternative anxiolytic drug had to be present as well.

In order to exclude patients with severe disorders, a total score of at least 12 points in a verbal multiple-choice intelligence test based on vocabulary (MWT-B; Lehrl 1977) and a total score not exceeding a 14 points maximum on the Hamilton Anxiety Scale (HAMA; Hamilton 1976) were required upon enrollment. In addition, eligible patients also had to be able to complete the self-evaluation scales.

Exclusion criteria included other anxiety disorders and psychiatric diseases, suicidal tendencies, drug abuse or addiction, severe physical illnesses, need of medical treatment which could interfere with the evaluation of efficacy, constitutional hypotension, ocular disorders, known allergies to kava extract and lactose intolerance. Furthermore, pregnant or nursing mothers and patients who were participating in another study simultaneously or up to 4 weeks prior to the start of treatment were also excluded.

Study design

The clinical trial was planned and conducted as a prospective, randomized, placebo-controlled, double-blind study with parallel groups and an adaptive interim analysis. To ensure equal patient numbers in both study groups, the trial participants were assigned to the double-blind treatments in balanced random blocks, in the order of their inclusion. The random code was kept under lock and seal and was not disclosed before close of database.

The double-blind treatment phase extended over 5 weeks. The study medication was available in capsules filled with either 50 mg of dry extract standardized to 35 mg kava lactone, or placebo. Both drugs were identical in all aspects of their appearance. During the first week, the daily dose was gradually increased from 50 mg to 300 mg (3×2 capsules per day). Simultaneously, the pre-existing benzodiazepine treatment with lorazepam, bromazepam, alprazolam or oxacepam, which had been given with an individually titrated, constant dosage during at least 2 weeks prior to randomization, was tapered off at a steady rate over the first 2 weeks of double-blind treatment (at day 7, the benzodiazepine dosage had to be reduced by at least 50%; the patients were aware that the benzodiazepine medication was being tapered off). These initial dosage adjustments were followed by 3 weeks of anxiolytic treatment with the study medication alone.

The treatment phase was followed by a 3-week follow-up phase, at the end of which the patients were re-examined. During follow-up, which was intended as a withdrawal trial, patients whose overall HAMA score had improved (i.e. decreased) during the treatment phase received placebo medication and patients whose score was unchanged or had increased were given adequate anxiolytic treatment according to the clinical judgment of the investigating physician (the protocol did not impose any restrictions regarding the choice of drugs or dosage).

The primary outcome measures of the trial were the differences in the overall scores of the Hamilton Anxiety Scale (HAMA) and the "Befindlichkeits-Skala" (Bf-S – subjective well-being scale) (CIPS 1996) between enrollment into the trial and the end of the treatment phase, as well as the incidence of benzodiazepine withdrawal symptoms during the double-blind treatment phase. Withdrawal phenomena were assessed by questioning the investigator for specific (e.g. disturbed perception), severe (e.g. delirium) and non-specific symptoms (e.g. tremor, increased sweating). In the case of withdrawal effects, a comprehensive description was obtained.

Secondary measures used to evaluate the efficacy of the preparations were obtained from the "Erlanger Angst und Aggressions-Skala" (EAAS – Erlangen Anxiety and Aggression Scale) (S. Lehrl, personal communication) and the Clinical Global Impressions (CGI) (National Institute of Mental Health 1976). At the beginning and end of double-blind treatment the investigator also rated the prognosis for each patient's course of disease as good, moderate or poor. Treatment safety was assessed by interview, by recording of adverse events during the course of the trial and by monitoring laboratory variables (ESR, hemoglobin, hematocrit, erythrocytes, leukocytes, thrombocytes, Quick's test, GPT, γ-GT and creatinine as well as urine values for erythrocytes, pH, proteins, glucose, nitrites and ketone bodies) at the start of the trial and at the end of double-blind treatment.

In order to control a multiple type I error level of α=0.05 in the presence of multiple primary endpoints, the null hypotheses describing the treatment group differences to be tested during confirmatory analysis were arranged in the protocol by descending order importance: (1) HAMA total score; (2) subjective well-being (Bf-S); (3) incidence of benzodiazepine withdrawal symptoms.

The application of the corresponding multiple test procedure, according to which less important hypotheses are only tested after all more important null hypotheses have been rejected, ensures the control of a multiple level of α (Maurer et al. 1995; Kieser et al. 1999). Hypotheses (1) and (2) were tested using the Wilcoxon-Mann-Whitney *U*-test, while Fisher's exact test was applied for hypothesis (3).

After 40 patients had completed the trial, a planned, adaptive interim analysis (Bauer and Köhne 1994) was carried out. This design permits the termination of a trial after the interim evaluation, or its continuation following a re-estimation of the sample size, depending on the results of the analysis. In order to control a type I error of $\alpha=0.05$ for the entire trial, the level of significance for the interim analysis was 0.0207 (Bauer and Köhne 1994).

The confirmatory statistical analysis was undertaken according to the intention-to-treat-principle, with the inclusion of all randomized patients. Missing values were replaced by the last previous non-missing value using the last-observation-carried-forward procedure. In accordance with the specification of the hypotheses in the study protocol, all confirmatory tests for the outcome measures were performed one-tailed (in order to reflect the study's intention to demonstrate superiority of WS®1490 over placebo). All other *P*-values are descriptive and reported two-tailed. The statistical analysis was performed with the SAS statistical analysis system, version 6.11, on a personal computer running under MS Windows 3.11.

The study was carried out in accordance with the GCP recommendations and the Declaration of Helsinki. A positive vote of the appropriate ethics committees was obtained prior to the start of the study. All study participants gave their written informed consent prior to their inclusion into the trial.

Results

Sample characteristics and analysis populations

Forty male or female, adult out-patients were included into the trial, 20 of whom were randomized to treatment with WS®1490 and 20 to placebo. Twenty-five study participants were male and 15 female, with an average age of 40 years (range 21–75 years). The most frequent diagnoses of anxiety states were generalized anxiety disorder (13 cases), social phobia (14 cases) and simple phobia (11 cases). Table 1 shows that at the start of double-blind treatment, the study groups were well balanced with regard to demographical and anthropometrical characteristics as well as the primary outcome measures (HAMA and Bf-S total scores). There were also no rele-

vant differences regarding previous and concomitant medication.

As regards previous benzodiazepine medication, the use of specific drugs of this class was comparable in both treatment groups: ten patients randomized to WS®1490 (50%) and 12 patients in the placebo group (60%) took lorazepam and six (30%) in each treatment group bromazepam; the remaining study participants received oxazepam or alprazolam. For lorazepam, the dosage varied between 2 and 4 mg/day in both treatment groups, with the majority of patients receiving 3 mg/day. Bromazepam was mostly administered at a dose of 6 mg/day, with individual patients receiving 4 or 12 mg/day. No relevant differences were observed between the treatment groups. Prior to entering the trial, the patients had received uninterrupted medication with benzodiazepines at an unchanged dosage for at least 4.5 weeks, with mean durations of 20 months in the WS®1490 group and 22 months in the placebo group. The maximum duration of benzodiazepine pretreatment was 13 and 7 years for WS®1490 and placebo, respectively.

Out of the 40 patients included, 37 completed the study according to plan. Three participants (WS®1490: 2; placebo: 1) terminated the trial prematurely because of the occurrence of withdrawal symptoms after long-term benzodiazepine treatment, without a causal relationship to the test substance. None of the patients who completed the trial as scheduled showed relevant protocol violations concerning observance of the examination schedule or drug compliance. For one study participant in the WS®1490 group, no indisputable diagnosis of the anxiety disorder in accordance with the inclusion criteria was documented, which was rated as a major protocol violation. The intention-to-treat (ITT) population included all randomized patients (WS®1490: 20; placebo: 20). The additional per-protocol analysis of treatment efficacy comprised the 36 patients (WS®1490: 17; placebo: 19) without premature discontinuation or relevant protocol deviations.

Primary outcome measures

During the course of randomized treatment, the WS®1490 group showed a marked and monotonic decrease of the HAMA total score, with a median improvement of 7.5 points between baseline and treatment end (Table 2). A beneficial treatment effect was already visible after one week on WS®1490 (Fig. 1). On the other hand, no comparable improvement was found in the placebo group, where the median HAMA total scores during double-blind treatment varied unsystematically around the baseline level (treatment end: deterioration by 1 point). The treatment group comparisons showed two-tailed *P*-values <0.05 for the assessments on days 8, 22, 29 and 36 (or treatment end). In particular, the null hypothesis regarding the HAMD total score difference at treatment end was rejected ($P=0.01$; *U*-test, one-tailed).

Table 1 Baseline characteristics of the treatment groups (medians and ranges or absolute frequencies)

Variables	WS®1490 (*n*=20)	Placebo (*n*=20)
Sex (m/w) (*n*)	14/6	11/9
Age (years)	39.1 (20.8–74.4)	42.3 (24.8–74.6)
Height (cm)	174 (157–183)	168 (159–189)
Weight (kg)	75 (51–82)	67 (51–89)
DSM-III-R-diagnoses (*n*)		
300.02 (general anxiety state)	7	5
300.22 (agoraphobia)	–	2
300.23 (social phobia)	6	8
300.29 (simple phobia)	6	5
Other	1	–
HAMA total score	13 (10–14)	13 (11–14)
Bf-S total score	41 (33–52)	42.5 (34–51)
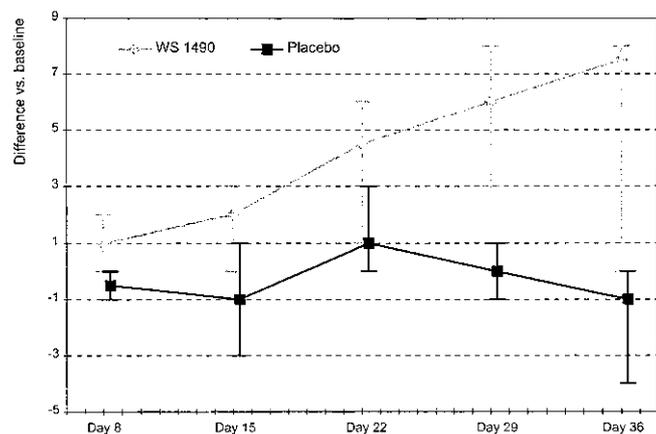
Fig. 1 Changes in the HAMA total score compared to the start of treatment (ITT population; medians with 95% confidence intervals; $P \leq 0.05$ for all treatment group comparisons except day 15)

Fig. 2 Changes in the Bf-S total score compared to the start of treatment (ITT population; medians with 95% confidence intervals; $P \leq 0.05$ for the treatment group comparisons at days 29 and 36)

Table 2 HAMA total score change during double-blind treatment (ITT population; medians with 95% confidence intervals; P-values: U-test, one-tailed)

HAMA difference	WS®1490 (n=20)[a]	Placebo (n=20)[a]	P-value
Day 1 to day 8	1 (0; 2)	−0.5 (−1; 1)	0.01
Day 1 to day 15	2 (0; 3)	−1 (−3; 1)	0.07
Day 1 to day 22	4.5 (1; 6)	1 (0; 3)	0.04
Day 1 to day 29	6 (3; 8)	0 (−1; 1)	0.01
Day 1 to day 36[b]	7.5 (0; 8)	−1 (−4; 0)	0.01

[a] Positive values indicate symptom improvement
[b] Confirmatory analysis

Table 3 Bf-S total score change during double-blind treatment (ITT population; medians with 95% confidence intervals; P-values: U-test, one-tailed)

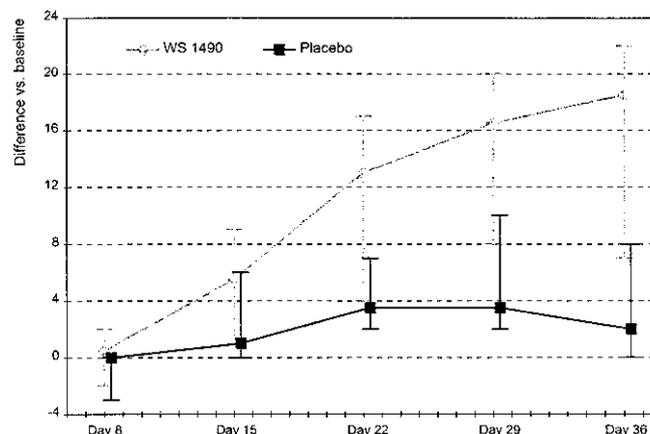| Bf-S difference	WS®1490 (n=20)[a]	Placebo (n=20)[a]	P-value
Day 1 to day 8	0.5 (−2; 2)	0 (−3; 0)	0.13
Day 1 to day 15	5.5 (1; 9)	1 (0; 6)	0.06
Day 1 to day 22	13 (4; 17)	3.5 (2; 7)	0.08
Day 1 to day 29	16.5 (8; 20)	3.5 (2; 10)	0.01
Day 1 to day 36[b]	18.5 (7; 22)	2 (0; 8)	0.002

[a] Positive values indicate symptom improvement
[b] Confirmatory analysis

In a supplemental responder analysis, treatment response was defined as a reduction of the HAMA total score by at least 50% compared to the start of treatment. According to this definition, there were 60% responders (12 out of 20) in the WS®1490 group and 20% (4 out of 20) in the placebo group (treatment group difference: $P=0.013$, two-tailed chi-square test).

The results for the second outcome measure, subjective well-being as assessed by the Bf-S total score, were comparable to those described for the HAMA: patients treated with WS®1490 showed a median improvement of 18.5 points during double-blind treatment, compared to 3 points in the placebo group (Fig. 2, Table 3). The superiority of WS®1490 was statistically significant at treatment end ($P<0.01$; U-test, one-tailed), with an additional descriptive, two-tailed P-value <0.05 in favor of WS®1490 on day 29.

During the course of the double-blind treatment phase, withdrawal symptoms were reported in eight (40%) patients under WS®1490 treatment and in 10 (52.6%) patients in the placebo group. The difference between the two treatment groups was statistically not significant ($P=0.32$; Fisher's exact test, one-tailed), so that the related null hypothesis could not be rejected.

The results of the per-protocol analysis were very similar to those of the intention-to-treat-analysis. In particular, the advantages for WS®1490 with regard to the differences between baseline and treatment end for the HAMA total score ($P<0.01$) and the Bf-S total score ($P<0.01$; one-tailed U-tests) were significant for this analysis population as well.

Secondary variables

Descriptive superiority of the WS®1490 group was shown for the Erlangen Anxiety and Aggression Scale (EAAS; $P=0.02$; U-test, two-tailed). During the course of treatment, patients receiving WS®1490 showed a reduction of the EAAS total score by 3.5 points (95% confidence interval, CI: 2; 5), compared to 0.5 points for placebo (CI: −1; 1). The analysis of item 1 (severity of illness) of the Clinical Global Impressions (CGI) showed a decrease in the perceived severity of the disorder under WS®1490 from a median of 5 (out of 7) points (patient is markedly ill; CI: 4; 5) at baseline to 3 points (patient is slightly ill; CI: 2; 5) at the end of treatment, whereas the severity in the placebo group remained unchanged at a

median of 5 points (CI baseline: 5; 5 – CI day 29: 4; 5). The associated descriptive *P*-value for the difference between the treatment groups was *P*=0.01 (*U*-test, two-tailed). For the change in the patients' overall condition (CGI item 2), a median of 2 points (condition is much improved; CI: 2; 4) was determined at treatment end for the WS®1490 group, compared to 4 points (condition is unchanged; CI: 3; 5) for the placebo group (*P*=0.02; *U*-test, two-tailed).

As regards the planned follow-up after randomized treatment, four patients in the WS®1490 group and 11 in the placebo group failed to show a reduction of their HAMA total score while under double-blind medication. In accordance with the study protocol, these patients were to be treated with anxiolytics during follow-up, according to the clinical judgement of the investigator. Two patients in the WS®1490 group were thus treated with doxepin during follow-up, one with trimipramin and the fourth was withdrawn from the study. In the placebo group, seven patients were treated with trimipramin, two with doxepin and one each with alprazolam and mianserin, respectively. Patients treated successfully during the double-blind phase received placebo during follow-up (withdrawal trial). Out of the total of 18 patients in the WS®1490 group who entered the follow-up phase, ten showed a recurrence (or persistence) of the basic symptoms of anxiety disorder after discontinuation of the study medication. Nine of these ten patients had been treated successfully with WS®1490 in the double-blind phase, and the tenth patient failed to show sufficient improvement under anxiolytic treatment as well, after not having responded favorably to WS®1490.

At the start of treatment, the investigator's prognoses for the patients' course of disease were balanced between the treatment groups. By the end of the double-blind treatment phase, ten patients in the WS®1490 group were indicated to have a good prognosis and only five had a poor prognosis. In the placebo group, however, four patients' prognosis was rated to be good, while 12 had a poor prognosis (*P*=0.06; chi-square test, two-tailed).

Tolerability and safety

During double-blind treatment, adverse events were observed in five patients under WS®1490 and ten patients in the placebo group. In all cases, these events were unspecific symptoms due to the withdrawal of benzodiazepine. (Specific benzodiazepine withdrawal symptoms, assessed by explicit patient questioning and presented in the section on treatment efficacy, were not counted as adverse events unless reported as such by the investigator.) No serious adverse events occurred during the entire trial. The comparison between the laboratory tests at the start and end of treatment showed no evidence of relevant changes.

Discussion

This trial demonstrates that kava special extract WS®1490 is significantly more effective than placebo in the treatment of moderately severe anxiety disorders of non-psychotic origin. With an onset of action already visible after one week (although benzodiazepine pretreatment was still being tapered off), the median value of the HAMA total score improved monotonically in the WS®1490 group, up to a 7.5-point decrease at treatment end, whereas the values remained essentially unchanged in the placebo group. For the HAMA total score, standard deviations of 7–9 points have been reported in the literature; an improvement by 7.5 points can therefore not only be regarded as statistically significant – it also demonstrates a clinically relevant effect (Beneke 1990; Hamilton 1976). With an improvement of the Bf-S total score of 18.5 points for WS®1490 compared to 3 points for placebo, the difference between the treatment groups lies in the region of about 1.5 SD (according to published data) and can thus be regarded as clinically relevant as well (CIPS 1996). The secondary variables measured on the EAAS and CGI scales support these results, as do the prognoses of the investigating physician. The fact that the patients treated with WS®1490, in contrast to those in the placebo group, showed a clear symptom alleviation in comparison to their condition at the end of benzodiazepine therapy indicates also that WS®1490 may have an anxiolytic effect beyond the benzodiazepines.

Following gradual discontinuation of the previous benzodiazepine treatment, withdrawal symptoms appeared in the placebo group slightly more frequently than in the WS®1490 group, without reaching the level of significant difference. When the trial medication was discontinued at the end of the treatment phase, none of the patients showed withdrawal symptoms. The slight difference between the treatment groups with regard to this outcome measure must be discussed in the light of the patients' histories: the study participants in the WS®1490 group had been suffering from an anxiety state for an average of 33 months, compared to 28 months in the placebo group. In the majority of patients, the pre-study benzodiazepine medication was started months before inclusion into the trial, in some cases years before trial enrollment. Given the duration of uninterrupted benzodiazepine pretreatment of up to 13 years, the low incidence of withdrawal symptoms in this study is in itself quite surprising. It was also interesting to note that during double-blind treatment and follow-up, none of the patients had to resume benzodiazepine treatment.

The above mentioned withdrawal symptoms of the patients were, without exception, slight psychomotor agitation and a minor tendency towards trembling of the hands during directed motility. In a retrospective review, the investigator rated these phenomena as less pronounced in the WS®1490 group. In addition, the patients of the WS®1490 group reported that they could cope much better with emotional strain in the examination

phase because they did not experience despondency and disgruntlement in contrast to their usual state before starting treatment with the study drug. However, these findings will need verification in a future study with suitable methods regarding the variables in question.

During the follow-up phase, the basic symptoms of anxiety disorder recurred in nine out of the 14 patients of the WS®1490 group who were switched to placebo (because their HAMA scores had improved under WS®1490)., This can be interpreted as additional evidence for the efficacy of the herbal extract (recurrence of symptoms after discontinuation of medication). One additional patient did neither respond to WS®1490, nor to the synthetic anxiolytic administered during follow-up. This leaves only two out of 20 patients randomized to WS®1490 whose symptoms could not be controlled by the study drug, but by a synthetic anxiolytic given during follow-up.

The tolerability of the study medications can be assessed as excellent. Adverse drug reactions to WS®1490 or placebo were not observed during the course of the trial; all adverse experiences were related to the withdrawal of benzodiazepine pretreatment.

Beyond confirming the anxiolytic effect of kava-kava special extract WS®1490, the results of the study also show that a further alleviation of many patients' anxiety state could be produced despite long previous treatment with benzodiazepines. This may either be attributed to the fact that these patients drew more benefit from treatment with WS®1490 than from benzodiazepines, or it could indicate a benzodiazepine tolerance effect. In the patients studied during this trial, withdrawal symptoms following discontinuation of benzodiazepines occurred somewhat less frequently under treatment with WS®1490, and even if they did occur, the anxiolytic effect remained. WS®1490 can thus be recommended as an efficacious and safe replacement for benzodiazepines in the treatment of anxiety disorders, although more subtle examinations with a differentiated observation of particular symptoms may be necessary to shed further light on its effect on benzodiazepine withdrawal symptomatology.

The benefits of WS®1490 are particularly important in case of long-term treatment and for patients with a high risk of dependency. In our study, the kava-kava special extract did not exhibit an addictive potential. This interpretation is supported by data from several other studies in which no addictive effects of kava-kava extracts were found at therapeutically effective dosages (e.g. Volz and Kieser 1997; Müller and Komorek 1999; Pittler and Ernst 2000).

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