DOUBLE-BLIND CLINICAL TRIAL OF A NATURAL KAVAPYRONE COMPLEX IN ELDERLY PATIENTS WITH ANXIETY SYNDROMES

Pietro de Nicola
Director of the Institute for
Gerontology and Geriatrics
University of Pavia, Italy

1989-1992

CLINICAL TRIAL MANAGEMENT

Responsible Person:
Prof. Dr. med. P. DE NICOLA †1993
represented by GIANNA DE NICOLA
Via Cavallini 15
27100 Pavia, Italy

CLINICAL TRIAL MONITORING
Responsible Person:
Dr.rer.nat. K.H. SENSCH
Kirchweg 11
82335 Berg, FRG

STATISTICAL ANALYSIS
Responsible Person:
Dr. med. J. SCHERER
Rosenbuschstr. 5
80538 München, FRG

TABLE OF CONTENTS

I. SUMMARY

Thirty-three patients with anxiety syndromes were treated with 200 mg kavapyrones/day (i.e. four 50 mg-kavapyrone capsules) and 36 patients received an underdosed regimen of kavapyrones at 20 mg/day (four 5 mg-capsules) (as a placebo replacement) in the framework of the present randomized, double-blind, parallel therapeutic trial carried out by Prof. de Nicola at the University Hospital for Gerontology in Pavia, Italy. The treatment groups were comparable with respect to all the initial (pretherapy) parameters. A test with the Hamilton Anxiety Scale was performed before the start of the therapy, on day 14 and on day 28 after therapy begin. Based on valid international practice, the Hamilton Total Score, the Hamilton Score for physical anxiety and the Hamilton Score for psychological

anxiety were enlisted to assess the therapeutic efficacy. In addition, the Physician Assessment of the preparation was analyzed by interferential statistics.

No difference in the tolerance could be found between the study medications. Regarding the efficacy in terms of the clinical symptoms, the superiority of the study drug (50 mg kavapyrones) was found to be statistically significant compared to the placebo preparation (5 mg kavapyrones). The difference between the drug groups and the placebo group was significant already as of treatment day 14 - both with respect to the Hamilton Anxiety Total Score as well as the Hamilton Scores for physical and psychological anxiety. A significant difference could be seen between the treatment groups also on day 28, demonstrated by the analysis of the Hamilton Anxiety Scale as well as by the Global Physician Assessment at the end of the study. The therapeutic success was not found to be gender-dependent.

Therewith, administration of 200 mg kavapyrones/day proved to be effective for the treatment of anxiety (anxiolytic effect) in the present placebo-controlled, double-blind trial. This conclusion applies for the psychological components of anxiety as well as for the physical components. The data demonstrate further that the preparation exerts a stronger effect on the psychological symptoms of anxiety than on the physical symptoms.

II. INTRODUCTION

The kava extract is obtained from the extraction of the rhizome of the kava plant (*ex Rhizoma Piperis methystici*) which contains kavapyrones as the active ingredients, among others methysticin, dihydromethysticin, kavain, dihydrokavain and yangonin (D.D. JAMIESON et al., SMITH, SMITH et al.).

Since centuries now, the natives of the South Sea Islands have made use of the pleasant relaxing effect of the kava drink (HÄNSEL 1959, 1964).

The relaxing, anxiolytic, calming and balancing effect of kavapyrones has been long recognized and proven many times over in modern scientific investigations.

Pharmacology of Kavapyrones

Kavapyrones exhibit a broad spectrum of pharmacological efficacy: They act on the central nervous system and also have peripheral sites of action. The pharmacological effect of kavapyrones was the topic of numerous scientific investigations in the past and is described thoroughly in the literature (CAPASSO/CALIGNANO, JAMIESON/DUFFIELD, KLEINSORGE/RAHLFS, KLOHS et al., KRETSCHMER 1970, KRETZSCHMAR/MEYER, MEYER 1962).

Animal studies demonstrate that kavapyrones have a central-sedating, muscle-relaxing as well as tranquilizing effect on the limbic system, but without impairing the concentration (DUFFIELD et al., KRETZSCHMAR/TESCHENDORF, MEYER/KRETZSCHMAR 1966, MEYER 1962, 1979). The peripheral effect of kavapyrones is expressed as a direct impairment of the muscular contractility as well as in a local-anaesthetizing effect (MEYER/KRETZSCHMAR 1969, SINGH).

Clinical Efficacy and Tolerance of Kavapyrones

When taken orally, kavapyrones exert an anxiolytic effect in humans suffering from anxiety syndromes, and have a stabilizing effect on the psyche. They calm and relax without tiring and improve the quality of sleep in healthy subjects (AMBROZI, BÖHLAU et al., DONA et al., EMSER/BARTYLLA, GERBER 1986, 1988, KINZLER et al., KLIMKE, KRACH, KRETSCHMER, 1970, 1974, 1983, KRUEGER/KELL, LEHMANN et al., LINDENBERG/PITULE-SCHÖDEL, MÖLLER/HEUBERGER, PIACENZA, SCHOLING/CLAUSEN, WARNECKE, WARNECKE et al. 1986, 1990).

Studies in healthy subjects as well as trials in numerous and different groups of patients demonstrate the good tolerance of kavapyrones as well as the lack of an addictive potential (DONA et al., ELTANAIHI, EMSER/BARTYLLA, GERBER 1988, HUN et al., KINZLER et al., KLIMKE, KRACH, KRETSCHMER 1983, KRYSPIN-EXNER, LEHMANN et al., LINDENBERG/PITULE-SCHÖDEL, MÖLLER/HEUBERGER, MÖLLER et al., RÜHLAND/WERNECKE, SCHLIACK, WARNECKE, WARNECKE et al. 1986, 1990).

Official German Kava Monograph

The numerous data on the efficacy and safety of the kavapyrones was acknowledged by the adoption of an official monograph for *Piperis methystici rhizoma* - kava-kava rhizome. This so-called positive monograph was drafted by one of the official commissions of the German Drug Institute of the Federal Ministry of Health. The monograph was published in the Federal Gazette No. 101 of June 1, 1990. The monograph states the effective dose of kavapyrone to be 60-120 mg/day.

Kavapyrones: high-dosed vs. low-dosed

Good therapeutic results could be achieved with high doses (210 mg/day) of kavapyrones in patients with states of anxiety, tension and excitement of non-psychotic genesis (KINZLER et al.) as well as in menopausal patients with psychosomatic dysfunction (WARNECKE).

In 1993, H. VOLLMER wrote in the DAZ (Deutsche Arzneimittel Zeitung) under the heading "Arzneimittel im Gespräch" = "Drugs under Discussion": "Kava-kava has shown itself to be a possible alternative to the classical anxiolytics for the therapy of mild forms of anxiety syndrome. The prerequisite is that kava-kava be dosed high enough in the region of 210-240 mg/day."

The present study investigates the anxiolytic effect of kavapyrones - high-dosed vs. low-dosed - in elderly patients. The expected therapeutic efficacy of 200 mg/day is to be compared to the possible lack of efficacy of 20 mg kavapyrones/day. In this case, the justified assumption regarding the effective dose may also be confirmed at the same time in this study - namely that the dose range of 60-120 mg kavapyrones/day - as is stated in the monograph - is set too low.

III. METHODS

1. STUDY AIM

The aim of the study was to compare the efficacy and tolerance of the two dosages **200 mg kavapyrones/day and 20 mg kavapyrones/day as a placebo substitute** in patients with an anxiety syndrome.

2. STUDY DESIGN

The present study is a double-blind, randomized and placebo-controlled unicentre trial with two parallel test groups **(50 mg kavapyrones and 5 mg kavapyrones as a placebo substitute)** and a fixed dosage regimen **(2 x 2 capsules/day).** The patients were treated with one of the two study preparations in accordance with the study protocol and under the direction of Prof. de Nicola at the University Hospital for Gerontology in Pavia.

3. TEST PREPARATIONS

- Kavapyrone preparation 50* as the study drug:
  One hard gelatin capsule contains:
  50 mg kavapyrones (*ex Rhizoma Piperis Methystici*)

- Kavapyrone preparation 5 as the placebo substitute:
  One hard gelatin capsule contains:
  5 mg kavapyrones (*ex Rhizoma Piperis Methystici*)

* Commercial preparation: Kavasedon® Capsules,
Manufacturer: Harras-Pharma-Curarina GmbH

4. STUDY PLAN

Before the start of therapy on study day 0, an anamnesis was recorded, a physical examination was performed, a physician assessment with the Hamilton Anxiety Scale (HAMA) was carried out and a self-assessment (patient assessment) with the State Trait Anxiety Inventory (STAI) Scale was performed. The Hamilton Anxiety Scale is an assessment scale used to evaluate states of anxiety. It is intended for patients in whom a neurotic anxiety state has already been diagnosed. The HAMA, STAI and screening of adverse drug effects (adverse events: AE) were carried out on day 14. A physical examination, the HAMA, STAI and AE-screening were carried out on day 28, i.e. at study completion, as was also a pill count to monitor the drug compliance.

5. PATIENT SELECTION

A total of 70 hospitalized patients were admitted to the study. Of these, 33 patients in the drug group and 36 patients in the placebo group could be evaluated. All the patients were older than 40 years of age.

5.1 Inclusion Criteria according to the Study Protocol

- The pretrial HAMA Score had to have been at least 15.
- States of anxiety which are characterized as follows (Guidelines for the clinical evaluation of anti-anxiety drugs): The patients must exhibit manifestations 1 and 2 with at least moderate intensity as well as three other of the symptoms named under 3 - 17.

Subjective Symptoms

1. Nervous, shaky, distracted feeling
2. Fearful, timorous, oppressive, panicky feeling
3. Fear of falling over/fainting, of screaming, of losing control of one's self, of large crowds of people, of places, of disaster or of death
4. Avoidance of certain places, things or activities because of anxiety
5. Tense or overexcited feeling, muscular or motor phenomena
6. Tense, painful muscles
7. Shivering, shaking
8. Restlessness, fidgetiness

Autonomic Phenomena

9. Tachycardia or palpitations, breast pain
10. Difficulty in breathing, gasping for breath, feeling of suffocation, lump in the throat, choking
11. Sweating, particularly in the armpits, palms of the hands, soles of the feet
12. Cold, sweaty hands
13. Dry mouth
14. Rotary vertigo, unconsciousness (fainting), dizziness, weakness
15. Tingly sensation in the hands or feet
16. Gastric flatulence, nausea, indigestion
17. Frequent urge or urgency to pass water/stools

5.2 Exclusion Criteria according to the Study Protocol

Patients with severe diseases of the liver and kidney, cardiovascular system, gastrointestinal tract, haemopoietic and endocrine systems were excluded from participating in the study, as were also persons with known drug, alcohol and medication abuse as well as intoxications. Other exclusion criteria included anxiety due to organic diseases - psychoses and severe behavioral disorders - symptomatic transitory psychotic syndrome - pretreatment in the preceding four weeks or concomitant

therapy with hypnotics, antidepressives, neuroleptics, reserpine, beta-blockers, antihistamines, antiemetics, initial dose-setting or switch-over of antihypertensives - as well as pregnancy or the lactation period.

6. DOSAGE

The dosage of both test preparations was 2 x 2 capsules/day - corresponding to 2 x 100 mg kavapyrones/day and - as a placebo substitute - 2 x 10 mg kavapyrones/day. The capsules were taken together with some liquid at meals in the morning and evening.

7. CONCOMITANT MEDICATION

Existing (concomitant) medication at the start of the study was permitted during the study as needed, as long as it did not fall under the exclusion criteria. Prerequisite: The medication was well-tolerated hitherto and was continued without any significant change made to the dosage.

8. ASSESSMENT OF THE EFFICACY

Only the test with the **HAMA Scale** and the **Physician Assessment** were chosen as the main study variables to compare the efficacy. There are grounds to assume that the test with the STAI Scale was not performed correctly, therewith leading to conspicuously favourable results for the preparation.

The items in the Hamilton Scale were summed up as a score for physical anxiety and as a score for psychological anxiety. The sum of the two subscores represents the HAMA Total Score. Both the two subscores as well as the total score were tested by an analysis of variance in order to assess the efficacy. As is common international practice, each item was not analyzed separately.

IV. RESULTS

A. Patient Collective

1. Demographic Data

Included in the study were 36 women (16 in the drug group and 20 in the placebo group) and 33 men (17 in the drug group and 16 in the placebo group). Nine patients were single, 51 were married and eight were widowed.

	Group		Total
	Kavapyrones 50 mg	**Kavapyrones 5 mg**	
Sex			
M	17 51.5%	16 44.4%	33 47.8%
F	16 48.5%	20 55.6%	36 52.2%
Marital Status			
Single	4 12.5%	5 13.9%	9 13.2%
Married	22 68.8%	29 80.6%	51 75.0%
Widowed	6 18.8%	2 5.6%	8 11.8%
Total	32 100%	36 100%	68 100%

Demographic Data

Statistical Analysis: Chi-square test

The chi-square test shows that no significant difference exists between the groups with respect to gender. The two treatment groups are, therewith, comparable.

The patients' age ranged between 48 and 82 years, and the mean age was approx. 68 years. The mean age for the drug group and for the placebo group was 68 years.

The patients' height ranged between 61 cm and 180 cm, and the mean value in the drug group was 166 cm and 164 cm in the placebo group.

The body weight ranged between 50 kg and 176 kg with a mean value of 64 kg for the drug group and 73 kg for the placebo group.

	Group		Total
	Kavapyrones 50 mg	**Kavapyrones 5 mg**	
Age			
Mean	67.85	67.64	67.74
Minimum	57.00	48.00	48.00
Maximum	82.00	76.00	82.00
Standard Deviation	4.58	5.06	4.80
N	33	36	69
Height			
Mean	166.03	163.71	164.84
Minimum	154.00	61.00	61.00
Maximum	180.00	180.00	180.00
Standard Deviation	4.74	18.53	13.65
N	33	35	68
Weight			
Mean	63.74	72.67	68.46
Minimum	55.00	50.00	50.00
Maximum	75.00	176.00	176.00
Standard Deviation	5.01	29.38	21.97
N	32	36	68

Age, Height, Weight

Statistical Analysis by Analysis of Variance

The analysis of variance shows that the two treatment groups are comparable in terms of the criteria age, height and body weight.

2. Anamnestic Data

Previous Occurrence of the Anxiety Disorder

As expected, the anxiety disorder was most frequently experienced in phases. One patient experienced a recent deterioration in his disease, and one patient considered his anxiety syndrome to differ from an earlier state of anxiety. For most of the patients, the disease state was a recurrence of a known anxiety disorder.

Start of the Current Anxiety Disorder

The current condition began in over 95% of the patients three to six months prior to the start of the study.

	Group		Total	
	Kavapyrones 50 mg		**Kavapyrones 5 mg**	
Description of Condition				
Deterioration	0	.0%	1	2.8%	1	1.4%
Recurrence	32	97.0%	35	97.2%	67	97.1%
Different from earlier	1	3.0%	0	.0%	1	1.4%
Begin						
3 to 6 months	32	97.0%	34	94.4%	66	95.7%
6 months to 1 year	1	3.0%	2	5.6%	3	4.3%
Total	33	100%	36	100%	69	100%

Anamnesis

The treatment groups are comparable with respect to these two anamnestic parameters.

Earlier Drug Treatment of the Anxiety Disorder

Only one patient did not receive any drug therapy for earlier exacerbations of the anxiety disorder.

	Group		Total
	Kavapyrones 50 mg	**Kavapyrones 5 mg**	
No pretreatment	0 .0%	1 2.8%	1 1.4%
Medications	33 100%	35 97.2%	68 98.6%
Total	33 100%	36 100%	69 100%

Treatment of an Earlier Anxiety Disorder

3. Severity of the disease

The two therapy arms did not differ with respect to the severity of the disease prior to study begin.
The drug group had a mean HAMA Scale Score of 27.55 and the mean value for the placebo group was 29.95. The possible maximal value of the Hamilton Anxiety Scale with 14 items is 56.

	Group		Total
	Kavapyrones 50 mg	**Kavapyrones 5 mg**	
HAMA Day 0			
Mean	27.55	29.25	28.43
Minimum	16.00	22.00	16.00
Maximum	35.00	35.00	35.00
Standard Deviation	4.60	3.34	4.05
N	33	36	69

Pretherapy Hamilton Anxiety Total Score

The two groups are comparable in terms of the severity of the disease prior to therapy.

B. CLINICAL EFFICACY

1. Physician Assessment of the Course of the Disease with Therapy

1.1 Hamilton Score for Physical Anxiety

The Hamilton Score for physical anxiety is significantly different between the two treatments over the course of therapy.

With comparable initial values of 10.91 in the drug group and 11.92 in the placebo group, the mean HAMA Score for physical anxiety in the placebo group remains practically constant over the three measurement times. In contrast, the value in the drug group drops distinctly and significantly from 10.91 to 7.58 on treatment day 14 and then further to 6.79 on treatment day 28.

	Group		**Total**
	Kavapyrones 50 mg	**Kavapyrones 5 mg**	
HAMA Physical Day 0			
Mean	10.91	11.92	11.43
Minimum	2.00	5.00	2.00
Maximum	15.00	16.00	16.00
Standard Deviation	3.19	2.59	2.91

N	33	36	69
HAMA Physical Day 14			
Mean	7.58	11.28	9.51
Minimum	1.00	5.00	1.00
Maximum	15.00	16.00	16.00
Standard Deviation	2.94	2.81	3.41
N	33	36	69
HAMA Physical Day 28			
Mean	6.79	10.36	8.65
Minimum	1.00	3.00	1.00
Maximum	17.00	15.00	17.00
Standard Deviation	3.02	3.38	3.66
N	33	36	69

Physical Anxiety

Physical Anxiety

Kavapyrones 50 mg
Kavapyrones 5 mg

HAMA Physical

Day

Statistical Analysis: Analysis of Variance - **Physical Anxiety** Day 0 vs. Day 14

The two treatment groups differ significantly already on day 14 (Analysis of variance - physical anxiety, day 0 vs. day 14; null hypothesis: The change (decrease) in the HAMA Score for physical anxiety does not differ between the two groups; group by time, p = 0.000).

Analysis of Variance - **Physical Anxiety** Day 0 vs. Day 28

The two treatment groups differ significantly also on day 28 (Analysis of variance - physical anxiety, day 0 vs. day 28; null

hypothesis: The change (decrease) in the HAMA Score for physical anxiety does not differ between the two groups; group by time, p = 0.002).

Analysis of Variance - **Physical Anxiety** Day 14 vs. Day 28

The two treatment groups do not differ significantly from one another between day 14 and day 28 (Analysis of variance - physical anxiety, day 14 vs. day 28; null hypothesis: The change (decrease) in the HAMA Score for physical anxiety does not differ between the two groups; group by time, p = 0.837).

Analysis of Variance - **Physical Anxiety** over the Entire Treatment Period

The analysis of variance carried out for the entire study period - i.e. days 0, 14, 28 - likewise shows for the time course a significant difference between the two treatment groups. (Analysis of variance - physical anxiety, day 0, day 14, day 28; null hypothesis: The change (decrease) in the HAMA Score for physical anxiety does not differ between the two groups; group by time, p = 0.0000).

Analysis of Variance - **Physical Anxiety** with Respect to Gender

The gender plays no role in the preparation's therapeutic success: No significant difference is seen between males and females with regard to the course of the HAMA Score for physical anxiety. (Analysis of variance - physical anxiety, day 0, day 14, day 28 with respect to gender; null hypothesis: The change (decrease) in the HAMA Score for physical anxiety does not differ between the two groups; group by sex by time, p = 0.914).

1.2 Hamilton Score for Psychological Anxiety

The Hamilton Score for psychological anxiety is significantly different between the two treatments over the course of therapy.

With comparable initial values of 16.64 in the drug group and 17.33 in the placebo group, the mean HAMA Score for

psychological anxiety in the placebo group hardly changes over the three measurement times. In contrast, the value in the drug group drops distinctly and significantly from 16.64 to 11.48 on treatment day 14 and then further to 9.33 on treatment day 28.

	Group		Total
	Kavapyrones 50 mg	**Kavapyrones 5 mg**	
HAMA Psychological Day 0			
Mean	16.64	17.33	17.00
Minimum	13.00	13.00	13.00
Maximum	20.00	20.00	20.00
Standard Deviation	1.97	1.71	1.86
N	33	36	69
HAMA Psychological Day 14			
Mean	11.48	16.58	14.14
Minimum	7.00	7.00	7.00
Maximum	19.00	19.00	19.00
Standard Deviation	2.93	3.66	4.18
N	33	36	69
HAMA Psychological Day 28			
Mean	9.33	14.92	12.25
Minimum	6.00	6.00	6.00
Maximum	21.00	19.00	21.00
Standard Deviation	4.38	4.57	5.26
N	33	36	69

Psychological Anxiety

Psychological Anxiety

Kavapyrones 50 mg
Kavapyrones 5 mg

HAMA Psychological

Day

Statistical Analysis: Analysis of Variance - **Psychological Anxiety** Day 0 vs. Day 14

The two treatment groups differ significantly already on day 14 (Analysis of variance - psychological anxiety, day 0 vs. day 14; null hypothesis: The change (decrease) in the HAMA Score for psychological anxiety does not differ between the two groups; group by time, p = 0.000).

Analysis of Variance - **Psychological Anxiety** Day 0 vs. Day 28

The two treatment groups differ significantly also on day 28 (Analysis of variance - psychological anxiety, day 0 vs. day 28; null hypothesis: The change (decrease) in the HAMA Score for psychological anxiety does not differ between the two groups; group by time, p = 0.000).

Analysis of Variance - **Psychological Anxiety** Day 14 vs. Day 28

The two treatment groups do not differ significantly from one another between day 14 and day 28 (Analysis of variance - psychological anxiety, day 14 vs. day 28; null hypothesis: The change (decrease) in the HAMA Score for psychological anxiety does not differ between the two groups; group by time, p = 0.635).

Analysis of Variance - **Psychological Anxiety** over the Entire Treatment Period

The analysis of variance carried out for the entire study period - i.e. days 0, 14, 28 - likewise shows for the time course a significant difference between the treatment groups. (Analysis of variance - psychological anxiety, day 0, day 14, day 28; null hypothesis: The change (decrease) in the HAMA Score for psychological anxiety does not differ between the two groups; group by time, p = 0.0000).

Analysis of Variance - **Psychological Anxiety** with Respect to Gender

No significant difference is seen between males and females regarding the course of the HAMA Score of psychological anxiety. (Analysis of variance - psychological anxiety, day 0, day 14, day 28 with respect to gender; null hypothesis: The change (decrease) in the HAMA Score for psychological anxiety does not differ between the two groups; group by sex by time, p = 0.306).

1.3 Hamilton Anxiety Total Score

The significant superiority of the drug preparation compared to placebo is seen also in the HAMA Total Score.

With comparable initial values of 27.55 in the drug group and 29.25 in the placebo group, the mean HAMA Total Score in the placebo group does not essentially change over the three measurement times. In contrast, the value in the drug group drops distinctly and significantly from 27.55 to 19.06 on treatment day 14 and then further to 16.12 on treatment day 28.

	Group		Total
	Kavapyrones 50 mg	**Kavapyrones 5 mg**	
HAMA Day 0			
Mean	27.55	29.25	28.43
Minimum	16.00	22.00	16.00
Maximum	35.00	35.00	35.00
Standard Deviation	4.60	3.34	4.05
N	33	36	69
HAMA Day 14			
Mean	19.06	27.86	23.65
Minimum	9.00	14.00	9.00
Maximum	34.00	35.00	35.00
Standard Deviation	5.27	5.73	7.04
N	33	36	69

HAMA Day 28			
Mean	16.12	25.28	20.90
Minimum	8.00	11.00	8.00
Maximum	38.00	34.00	38.00
Standard Deviation	6.38	7.38	8.27
N	33	36	69

Hamilton Anxiety Total Score

Hamilton Anxiety Total Score

Kavapyrones 50 mg
Kavapyrones 5 mg

HAMA Total

Day

Statistical Analysis: Analysis of Variance - **Hamilton Anxiety Total Score** Day 0 vs. Day 14

The two treatment groups differ significantly already on day 14 (Analysis of variance - total score, day 0 vs. day 14; null hypothesis: The change (decrease) in the HAMA Total Score does not differ between the two groups; group by time, p = 0.000).

Analysis of Variance - **Hamilton Anxiety Total Score** Day 0 vs. Day 28

The two treatment groups differ significantly also on day 28 (Analysis of variance - total score, day 0 vs. day 28; null hypothesis: The change (decrease) in the HAMA Total Score does not differ between the two groups; group by time, p = 0.000).

Analysis of Variance - **Hamilton Anxiety Total Score** Day 14 vs. Day 28

The two treatment groups do not differ significantly from one another between day 14 and day 28 (Analysis of variance - total

score, day 14 vs. day 28; null hypothesis: The change (decrease) in the HAMA Total Score does not differ between the two groups; group by time, p = 0.815).

Analysis of Variance - **Hamilton Anxiety Total Score** over the Entire Treatment Period

The analysis of variance carried out also for the entire study period - i.e. days 0, 14, 28 - likewise shows for the time course a significant difference between the two treatment groups. (Analysis of variance - total score, day 0, day 14, day 28; null hypothesis: The change (decrease) in the HAMA Total Score does not differ between the two groups; group by time, p = 0.000).

Analysis of Variance - **Hamilton Anxiety Total Score** with Respect to Gender

No significant difference is seen between males and females regarding the course of the HAMA Total Score. (Analysis of variance - total score, day 0, day 14, day 28 with respect to gender; null hypothesis: The change (decrease) in the HAMA Total Score does not differ between the two groups; group by time by sex, $p = 0.567$).

2. GLOBAL PHYSICIAN ASSESSMENT AT STUDY COMPLETION

Statistical Analysis: Chi-Square Test

The study drug was also shown to be significantly superior in the global physician assessment of the therapeutic efficacy at the end of the study (chi-square test, $p = 0.00041$).

While the condition of 2/3 of the patients in the drug group were assessed by the physician as being "very much better", the condition of 2/3 of the patients in the placebo group was "unchanged" at the end of the study.

No therapeutic risks (adverse events) occurred in either of the two treatment groups.

	Group		Total
	Kavapyrones 50 mg	**Kavapyrones 5 mg**	
Therapeutic Efficacy			
not assessable	0 .0%	1 2.8%	1 1.4%
very much better	1 3.0%	0 .0%	1 1.4%
much better	23 69.7%	7 19.4%	30 43.5%
somewhat better	1 3.0%	3 8.3%	4 5.8%
unchanged	6 18.2%	24 66.7	30 43.5%
somewhat worse	2 6.1%	1 2.8%	3 4.3%
Therapeutic Risks (adverse events)			
none	33 100%	36 100%	69 100%
Total	33 100%	36 100%	69 100%

Physician Assessment

3. CLINICAL SYMPTOMS OF THE ANXIETY SYNDROME AT THE START OF TREATMENT AND OVER THE COURSE OF TREATMENT

The individual items of the HAMA Scale were not tested by interferential-statistical analysis.
Only a descriptive analysis of the course of the individual symptoms of the Hamilton Anxiety Scale is discussed in the following. The intensities of the individual items are expressed as "none", "mild", "moderate" and "severe".

3.1 Physical Anxiety, Individual Symptoms

The physical components of anxiety in the HAMA scale include muscular symptoms, sensory symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, urogenital symptoms and neurovegetative symptoms.

GROUP						Total
Kavapyrones 50 mg			Kavapyrones 5 mg			
DAY			Day			
0	14	28	0	14	28	
Muscular						
none						
mild						
moderate						
severe						
Sensory						
none						
mild						
moderate						
severe						
Cardiovascular						
none						
mild						
moderate						
severe						
Respiratory						
none						
mild						
moderate						
Gastrointestinal						
none						
mild						
moderate						
Urogenital						
none						
mild						
moderate						
Neurovegetative						
none						
mild						

3.2 Psychological Anxiety, Individual Symptoms

The psychological components of anxiety in the HAMA Scale include anxiousness, tension, fear, sleeplessness, impaired mental performance (cognitive function), depression and the behaviour at the interview.

GROUP						Total
Kavapyrones 50 mg			Kavapyrones 5 mg			
DAY			Day			
0	14	28	0	14	28	
Anxiousness						
mild						
moderate						
severe						
Tension						
mild						
moderate						
severe						
Fear						
none						
mild						
moderate						
severe						
very severe						
Sleeplessness						
none						
mild						
moderate						
severe						
very severe						
Impaired mental performance (cognitive function)						
mild						

moderate
severe

Depression
mild
moderate
severe

Behaviour at interview
none
mild
moderate

Hamilton: Psychological Anxiety, Individual Symptoms

4. PERCENTAGE CHANGES IN THE HAMA SCORE WITH THERAPY

The total score of the symptoms is formed by adding the single subscores for physical anxiety and psychological anxiety.

The percentage value expresses the percentage by which the score has decreased at each respective examination time.
The cumulative score at examination time "pretherapy" is set at 100%. The scores of the other times are then viewed in reference to the sum score.

An interferential-statistical analysis was not performed since the results of the statistical analysis of the percentage change in the cumulative score did not differ from the corresponding raw values.

	Group			
	Kavapyrones 50 mg		Kavapyrones 5 mg	
	DAY		DAY	
	14	28	14	28
HAMA Psychological				
Mean	-31.07	-41.96	-5.26	-14.38
Minimum	-53.33	-66.67	-58.82	-66.67
Maximum	5.56	21.43	5.88	5.88
Standard Deviation	15.57	30.81	16.50	23.91
N	33	33	36	36

HAMA Physical				
Mean	-28.72	-35.37	-4.64	-11.92
Minimum	-75.00	-81.82	-50.00	-81.25
Maximum	42.86	21.43	28.57	14.29
Standard Deviation	23.93	25.35	14.95	22.59
N	33	33	36	36
HAMA Total				
Mean	-30.44	-39.24	-5.13	-13.51
Minimum	-57.14	-72.41	-50.00	-68.57
Maximum	15.00	15.15	12.00	6.25
Standard Deviation	16.30	26.10	15.19	22.81
N	33	33	36	36

Hamilton: Percentage Changes with Therapy

The significantly greater decrease in the symptoms with the study drug compared to the placebo can be clearly recognized from the percentage changes in the individual cumulative scores.

The Hamilton Total Score is diminished by 30% with the study drug at examination time day 14 and by 39% at examination time day 28. Placebo treatment causes only a 5% and 13% reduction, respectively.

Similar results are seen for the subscore values for physical and psychological anxiety.

The data indicate that the preparation has a greater effect on the psychological components of anxiety than on the physical components.

C. TOLERANCE

Side effects occur rarely and are, therefore, difficult to ascertain with statistical methods in the framework of usual clinical trials.

Due to the magnitude of the beta error in this study, the present case makes its impossible to make a conclusive statement regarding the tolerance.

No side effects were observed in the present study.

Pavia, _____
Date

Berg, _____ Munich, _____
Date Date

CLINICAL TRIAL MANAGEMENT
Responsible Person:
Prof. Dr. med. P. DE NICOLA †1993
represented by GIANNA DE NICOLA
Via Cavallini 15
27100 Pavia, Italy

CLINICAL TRIAL MONITORING
Responsible Person:
Dr.rer.nat. K.H. SENSCH
Kirchweg 11
82335 Berg, FRG

STATISTICAL ANALYSIS
Responsible Person:
Dr. med. J. SCHERER
Rosenbuschstr. 5
80538 München, FRG

V. LITERATURE REFERENCES

L. AMBROZI: Therapiewoche **29**, 5967 (1979)

V. BÖHLAU et al.: Zeitschrift für präklinische Geriatrie Nr. **2** (1973)

A. CAPASSO, A. CALIGNANO: Acta Therapeutica **14**, 249-256 (1988)

G. DONA et al.: Therapiewoche **26**, 2836 (1986)

P.H. DUFFIELD et al.: Arch. int. Pharmacodyn. 301, 81-90 (1989)

S. ELTANAIHI: Deutsches Medizinisches Journal **20**, 635 (1969)

W. EMSER, K. BARTYLLA: TW Neurologie Psychiatrie **5**, 636-642 (1991)

B. GERBER: Naturheilpraxis Nr. **1**, 89 (1986)

B. GERBER: Erfahrungsheilkunde **3**, 170 (1988)

R. HÄNSEL: Deutsche Apotheker-Zeitung **99**, 1037 (1959)

(1964)

N. HUN et al.: Münchener Medizinische Wochenschrift **109**, 2197 (1967)

D.D. JAMIESON et al: Arch. int. Pharmacodyn. **301**, 66-80 (1989)

D.D. JAMIESON, P.H. DUFFIELD: Clinical and Experimental Pharmacology and Physiology **17**, 495-508 (1990a)

D.D. JAMIESON, P.H. DUFFIELD: Clinical and Experimental Pharmacology and Physiology **17**, 495-508 (1990b)

E. KINZLER et al.: Arzneim.-Forsch./Drug Res. **41** (I), Nr. 6, 584-588 (1991)

H. KLEINSORGE, V. RAHLFS: Arzneimittel-Forschung **19**, 623 (1969)

A. KLIMKE: "Die Wirksamkeit von D,L-Kavain zur Behandlung von neurotischer Angst, erlebnisreaktiven und psychovegetativen Störungen", Dissertation Düsseldorf (1988)

M.W. KLOHS et al.: Journal of Medicinal and Pharmaceutical Chemistry Vol. 1, 95-103 (1959)

H. DRACH: ZFA **62**, Nr. 29, 1028-1031 (1986)

W. KRETSCHMER: Münchener Medizinische Wochenschrift **112**, 154-158 (1970)

W. KRETSCHMER: Münchener Medizinische Wochenschrift **116**, 74 (1979)

W. KRETSCHMER: Ärztliche Praxis **35**, 2324 (1983)

R. KRETZSCHMAR, H.J. MEYER: Naunyn-Schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie Bd. **250**, 134 (1965)

R. KRETZSCHMAR, H.-J. TESCHENDORF: Chemiker Zeitung **98**, Nr. 1, 24-28 (1974)

H. KRÜGER, G. KELL: Therapiewoche **27**, 9417 (1977)

K. KRYSPIN-EXNER: Münchener Medizinische Wochenschrift **116**, 1557 (1974)

E.LEHMANN et al.: Pharmacophsychiat. **22**, 258-262 (1989)

D. LINDENBERG, H: PITULE-SCHÖDEL: Fortschr. Med. **108**, Nr. 2, 31/49-34/54 (1990)

H.J. MEYER: Arch. int. Pharmacodyn, **138**, 505-536 (1962)

H.J. MEYER: Drugs /DD. Efron et al., eds., New York. Raven Press 133-140 (1979)

H.J. MEYER, R. KRETZSCHMAR: Klinische Wochenschrift **44**, 902-903 (1966)

H.J. MEYER, R. KRETZSCHMAR: Arzneimittel-Forschung **19**, 617-623 (1969)

H.J. MÖLLER, L. HEUBERGER: MMW **131**, Nr. 37, 656-659 (1989)

H.J. MÖLLER, et al.: MMW **134**, Nr. 37, 587-590 (1992)

MONOGRAPH: Monograph: Piperis methystici rhizoma - Kava Kava Rhizome, Bundesanzeiger Nr. 101 v. 1.6.1990

F. PIACENZA: Zeitschrift für Therapie **6**, 347 (1971)

W. RÜHLAND, O. WERNECKE: Z. Alternsforsch. **29**, 311 (1975)

H. SCHLIACK: Hippokrates - Wissenschaftl. Medizin u. praktische Heilkunde im Fortschritt der Zeit **38**, 26 (1967)

W.E. SCHOLING, H.D. CLAUSEN: Medizinische Klinik **72**, Nr. 32/33, 1301-1306 (1977)

Y.N. SINGH: Journal of Ethnopharmacology **7**, 267-276 (1983)

R. SMITH et al.: Journal of Chromatography **283**, 303 (1984)

R. SMITH: Phytochemistry, Vol. **22**, Nr. 4, 1055 (1983)

H. VOLLMER: DAZ **133**, Nr. 16, 1446 (1993)

G. WARNECKE et al.: Med. Welt **37**, 1379-1383 (1986)

G. WARNECKE et al.: Z. f. Phytotherapie **11**, 81-86 (1990)

G. WARNECKE: Fortschr. Med. **109**, Nr. 4, 119/65-122/70 (1991)