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Insomnia: Are Valerian/Balm Combinations of Equal Value to Benzodiazepine?

[Original title: *Baldrian-Melisse-Kombinationen versus Benzodiazepin bei Schlafstörungen gleichwertig? Untersuchung im Schlaflabor an 20 Probanden*]

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With the help of neurophysiological investigation methods (sleep laboratory as described by Rechtschaffen) the properties of a high-dose valerian/balm preparation is tested using a benzodiazepine preparation (0.125 mg Triazolam) and placebo as references in 20 volunteers. In the group of bad sleepers, the plant-based preparation showed an effect comparable to that of the benzodiazepine preparation, as well as an increase in deep sleep stages 3 and 4. No daytime sedation or rebound phenomena were observed after intake of the valerian/balm preparation, and no restriction of concentration or physical performance was observed in both the Concentration Performance Test and in the Labyrinth Test.

Key words: *Sleep disorders, plant-based sedative, Valerian, Balm, sleep EEG, sleep architecture*

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Adverse reactions from benzodiazepines are avoided when a plant-based alternative is used

Sleep disorders are a confirmedly widespread symptom in the population. On the basis of epidemiological investigations, it is possible to assume that approximately a third of the adult population suffers from initial and/or continued sleep disorders, i.e. either difficulties in falling asleep or difficulties in staying asleep [2]. These disorders require treatment in approximately 15 % [8]. A study of our own carried out in general practices in Mannheim established that almost 20 % of the patients treated in this area were suffering from severe sleep disorders of the continuance type [6].

At least in the general practitioner's domain, the treatment of insomnias is a matter for benzodiazepines. Particularly in the case of long-term treatment with benzodiazepines, however, a whole series of risks and undesirable adverse reactions occur. A development of tolerance may occur, accompanied by a loss in hypnotic efficacy. In addition, there is a danger of habit-forming and drug-dependency [3]. There is a very real danger of discontinuance insomnia (i.e. a rebound effect [3]), particularly in the case of the frequently recommended benzodiazepine hypnotics of short-term effect [3]. And where benzodiazepine hypnotics of long-term effect are concerned, an undesirable daytime sedation may develop which is capable of produ8cing a restriction in concentration and performance ability (hang-over effect). In addition to this, benzodiazepines cause cahnges in sleep EEG and are able to produce a respiratory depression (see [3] for survey).

On the basis of these not inconsiderable possible risks where the taking of benzodiazepines is involved, the search for useful alternatives in the treatment of sleeping disorders now seems expedient. In spite of the fact that such drugs are frequently taken [1,5,7], the therapeutical application of plant-based preparations, especially pharmaceuticals containing valerian, has received little attention up to now as regards scientific evaluations.

Thus, within the framework of the present study, the influence of a new valerian/balm combination on the sleep of healthy volunteers was investigated. The test preparation (Euvegal® forte sugar-coated tablets, manufacturer: *Spitzner Arzneimittelfabrik/Pharmaceuticals GmbH, Ettlingen, FR Germany*) contains 160 mg valerian extract in aqueous/ethanolic dry extract as well as 80 mg balm (Melissa) extract in aqueous/ethanolic dry extract. No valepotriates are contained.

Table 1: Sleep parameters

	Euvegal		**Triazolam**	
	Placebo	Active subst.	Placebo	Active subst.
Sleep continuity				
sleep efficiency	86.5 ± 11.4	90.4 ± 11.4	87.9 ± 9.2	93.8 ± 3.1**
falling-asleep latency (min)	17.8 ± 10.9	16.4 ± 10.1	18.2 ± 12.4	11.9 ± 7.4*
no. of waking periods	12.6 ± 9.7	9.6 ± 5.4	11.5 ± 7.3	9.2 ± 6.1(*)
Sleep architecture				
awake stage in %	9.6 ± 11.2	5.9 ± 4.8*	8.1 ± 8.6	3.2 ± 2.7**
1 % stage	7.4 ± 4.1	7.6 ± 4.9	8.0 ± 5.0	6.6 ± 3.8(*)
2 % stage	52.3 ± 7.1	51.1 ± 9.5	51.6 ± 6.8	52.2 ± 10.1
3 % stage	7.0 ± 4.8	9.0 ± 4.2(*)	6.3 ± 4.1	8.6 ± 5.5*
4 % stage	1.4 ± 3.4	1.6 ± 2.6	1.7 ± 4.2	1.4 ± 2.3
REM stage in %	20.7 ± 6.5	21.3 ± 6.0	20.9 ± 6.4	22.3 ± 5.5

(*) $p < 0.10$, * $p < 0.05$ ** $p < 0.01$ (T test, bilateral)

In order to carry out an investigation sufficient to meet the high demands necessary, the effect of this valerian preparation was compared with the ffects produced both by placebo as well as by a reference preparation (0.125 mg Triazolam). According to our knowledge, this is the first time that a purely plant-based sedative has been objectively compared with a highly effective benzodiazepine preparation.

Apart from subjective and objective measurements of sleep quality, an additional stress experiment was also included to test whether there were any effects on subjective wellbeing as well as concetnration and performance through administration of the valerian/balm preparation.

Study design

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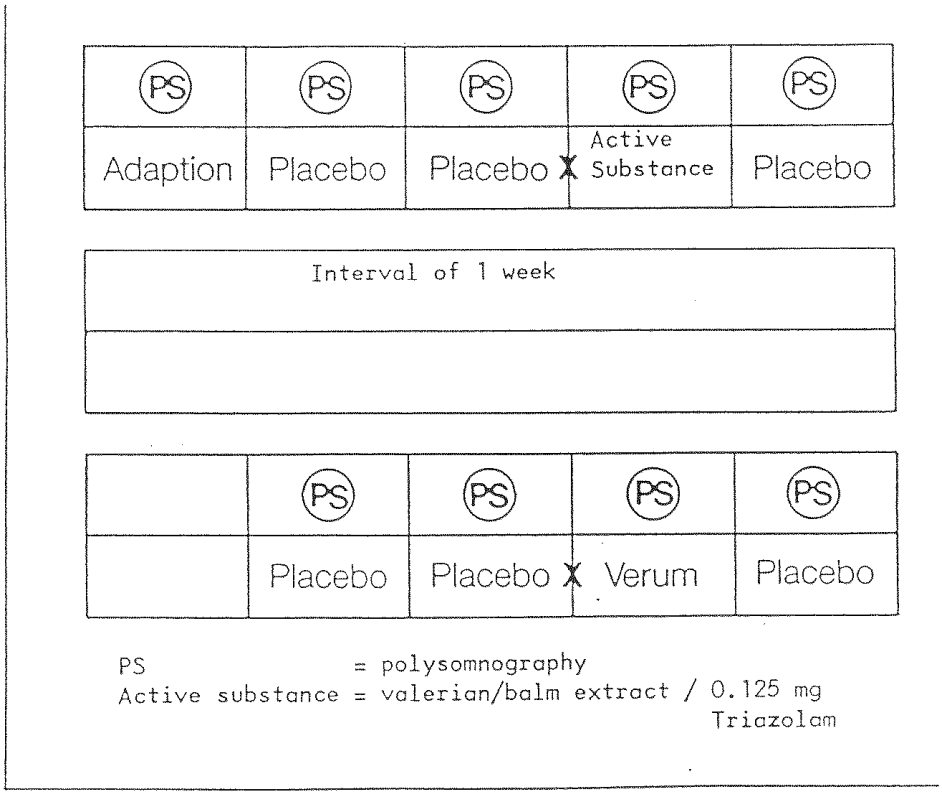
Participants

A total of 20 healthy volunteers aged between 30 and 50 years took part in the study; the mean age was 37.2 ± 5.9 years. Prior to inclusion in the study, the 10 male and 10 female participants were subjected to a comprehensive physical and psychiatric examination. Those volunteers with physical and/or psychiatric conditions as well as a family history with psychiatric diseases were excluded. In addition to this, routine laboratory parameters were determined and an ECG recording taken.

Fig. 1: Study design for Valerian/Balm extract versus Triazolam



Study progress

All volunteers were monitored for a total of 9 nights in the sleeping laboratory (see Fig. 1 for design). The study was carried out in two units; the first was for 5 nights, and the second consisted of four nights after a one-week interval immediately following the first unit. The first night in the sleep laboratory was used for adaptation to the new

surroundings and was therefore not applied in the second unit. In the subsequent nights, the participants received one casule and one sugar-coated tablet containing either placebo or active substance every night (double dummy method).

The active substance (valerian/balm preparation or Triazolam) was adminstered in the third/fourth or the seventh/eighth night in a cros-over design. As active substance, half of the participants received the valerian/balm preparation in the first trial unit, the other half received Triazolam. This process was correspondingly inversed in the second unit. After the two trial units, each participant had received each active substance once correspondingly. In order to be able to evaluate medicational effects independently of the temporal sequence of the application, the administration of active substance was additionally randomized in the third or fourth, otr the seventh or eighth night (Fig. 1).

In the test-free week between the first and second units, participants reported to be subjected to a stress test in the middle of the week. This test involved completikon of a Concentration-Performance Test (CPT) as well as the Labyrinth test [4]. For this phase of the trial, paricipants were randomized into a placebo and an active substance group (valerian/balm preparation only).

Before, during and after the trial, wellbeing (subjective condition status) and other psychopathological variables were recorded, and the heart rate continuouly monitored as a physiological parameter.

Recording of sleep

Sleep was recorded and evaluated on all 9 nights in accordance with the internationally recognized criteria established by Rechtschaffen and Kales [9]. The following characteristic parameters for sleep EEG were calculated from the visual evaluation thus conducted: sleep continuity, sleep architecture and REM sleep parameters [9].

Statistics

Descriptive stastics were for representation of mean values and standard deviations. Parametric procedures (ANOVA, t test) were used for interference statistics.

Tab. 1: Study design for valerian/Balm extract vs. Triazolam

	1	2	3	4	5	6	7
arith. mean	25.6	17.8	16.4	20.0	18.2	11.9	16.0
hrs. dev.	19.9	10.9	10.1	12.8	12.4	7.4	9.4
minimum	5.5	4.0	5.0	5.0	5.0	2.0	2.5
25 % percent	13.5	9.25	9.75	9.75	9.0	7.5	9.25
median	17.5	15.5	12.75	18.25	15.5	10.5	12.5
75 % percent	30.75	21.75	20.5	26.25	19.75	15.0	22.25
maximum	76.5	44.0	44.0	51.0	44.5	32.0	34.5

Table 3: Awake stage in percent of time in bed

	1	2	3	4	5	6	7
arith. mean	14.27	12.29	8.31	8.98	10.99	5.16	7.74
hrs. dev.	9.79	11.58	5.69	6.80	9.34	3.09	5.41
minimum	2.4	2.0	1.1	2.5	1.6	0.6	0.8
25 % percent	6.5	4.2	4.7	4.8	3.85	3.0	3.9
median	11.8	7.7	11.7	10.8	14.65	7.55	10.65
75 % percent	20.1	18.1	11.7	10.8	14.65	7.55	10.65
maximum	36.7	36.4	23.3	35.5	33.3	12.6	24.9

Table 4: Sleep efficiency (sleeping time in percent of time in bed)

	1	2	3	4	5	6	7
arith. mean	84.17	86.47	90.39	89.40	87.91	93.81	91.13
hrs. dev.	9.62	11.37	5.49	6.49	9.24	3.14	5.31
minimum	63.0	62.9	75.9	66.4	65.8	85.5	74.7
25 % percent	79.15	80.85	87.2	87.9	84.2	92.3	88.5
median	86.1	90.75	91.6	90.3	89.95	94.55	91.95
75 % percent	92.5	94.75	93.95	93.5	95.15	96.25	94.5
maximum	96.7	96.4	98.4	95.7	97.8	98.3	99.0

Legend to columns in Tables 2 - 4

1. Adaptation night
2. Placebo night before Euvegal 3. Active substance Euvegal
4. Placebo night after Euvegal
5. Placebo night before Triazolam 6. Active substance Triazolam
7. Placebo night after Triazolam

Results

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Table 1 shows the mean values and standard deviations for placebo and active substance separated according to valerian/balm preparation and Triazolam. In the case of Triazolam, there was a significant increase in sleep efficiency and a significant decrease in falling asleep latency. The awake stage was reduced, stage 2 was increases. The REM latency was significantly lengthened.

Due to a high interindividual and intraindividual variablility of sleep architecture and sleep quality, and the low number of participants, no significant effects were established for the prepatation tested under this evaluation method, although the mean values indicated a clear sleep-improving effect with an increase in sleep efficiency and a reduction of the awake periods and waking time (Tabs. 2-4; Figs. 2-3).

In a second evaluation step, the random sample of participants was subdivided into a group of »good« and a group of »bad« sleepers according to the median of sleep efficiency (for the placebo value).

Fig. 4 shows the results on the influence of the valerian/balm preparation, compared with placebo, on sleep efficiency, broken down into »good« and »bad« sleepers. In the group of good sleepers, there was a significant reduction of REM-phase sleep as well as a significant reduction in duration of the first REM phase. By contrast, after treatment with the test preparation, the group of »bad« sleepers showed a significant increase in sleep efficiency when compared with placebo, as well as a clear tendency to an increase of deep sleep, i.e. stages 3 and 4. In the same manner, there was a clear tendency to a reduction of REM density after administration of the valerian/balm preparation.

In Table 3 we can see the data for the concentration/performance test divided up according to placebo or valerian/balm preparation. The group of participants treated with the valerian/balm preparation showed significantly better results than the placebo-treated control group in two parameters of the concentration test, i.e. the error percentages and the error quotients. There was no difference between the two groups in the labyrinth test.

Discussion

As of yet, there are too few data available as regards the scientific evaluation of plant-based preparations, in particular of those pharmaceuticals which contain valerian. Three work groups have conducted scientific, placebo-controlled investigations on the efficacy of valerian/balm preparations on subjective and objective sleeping parameters in healthy participants [1,5,7]. In all studies, a mild effect valerian on the subjective assessment of sleep could be established although, as regards its effect on EEG recordings made during sleep, the investigations ware not uniform and only showed tendencies towards a positive effect of valerian. In these studies, only young, healthy sleepers were primarily investigated.

In the present study, in the selection of participants for the investigation, care was taken that a more elderly age range (i.e. 30 to 50 years) was included. This was to

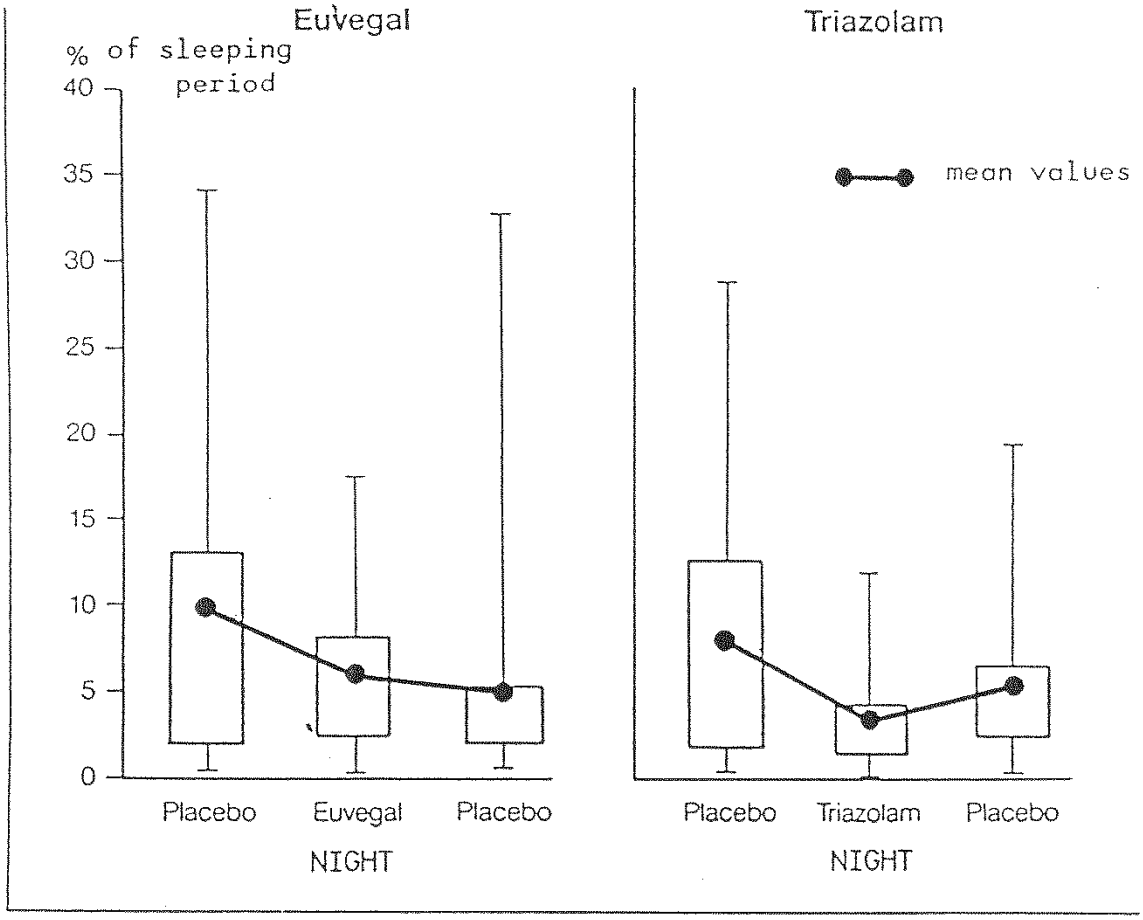
avoid - a procedure which seemed to have been usual in many studies up to now - the investigation of only young and healthy participants in whom initial sleep values were already in an optimum range anyway. Thanks to the design of the present study, we were thus able to guarantee that the medicational effects could be evaluated independently of the time sequence of administration. In addition to this, the effect of the new valerian/balm preparation was not only tested versus placebo in this study, but also versus a recognized hypnotic (Triazolam). Furthermore, an additional placebo night was added onto each section of the trial; the authors were thus in a position to check whether any hang-over or rebound effects occurred.

The first step in evaluation, i.e. the comparison between placebo and active substance values for both medicational forms produced the expected effect as regards Triazolam, i.e. an improvement of sleep efficiency and a reduction in the falling-asleep latency. In the context of this evaluation, there were clear tendencies in the expected direction where the valerian/balm preparation was concerned, which however could not be established statistically due to the high intraindividual and interindividual variability involved.

Increase of sleep efficiency in bad sleepers

A differentiation made on the median for sleep efficiency during the placebo night in good and bad sleepers showed that the valerian/balm preparation produces significant effexts with an increase in sleep efficiency and an increase in sleep stages 3 and 4 in the group of bad sleepers.

Fig. 2: Time spent awake in percent of sleeping period

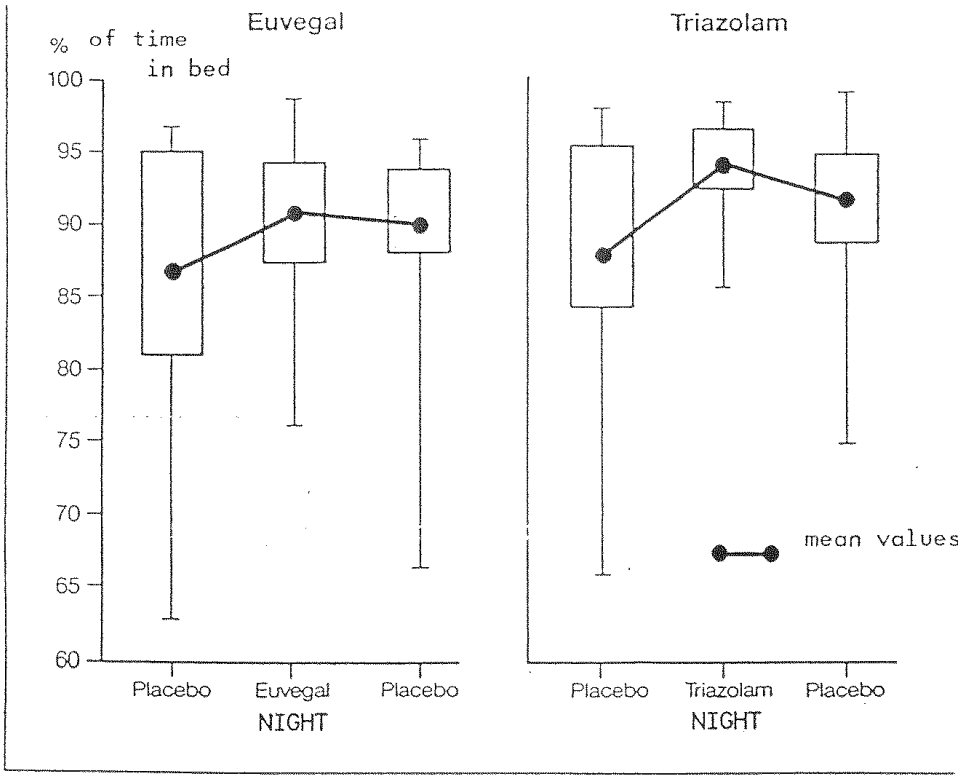


This differentiated analysis may be interpreted to the effect that no further sleep-improving effects are to be obtained with the valerian/balm preparation in the participants whose initial values are within the physiological range. Those volunteers, however, whose initial values were on a somewhat worse level, show an improvement in sleep after receiving the test preparation.

An increase in deep sleep stages such as those observed in this study have not been described in comparable publications.

In the assessment of the group of bad sleepers by themselves, the effects of the valerian/balm preparation are fully comparable with those of Triazolam.

Fig. 3: Sleep efficiency



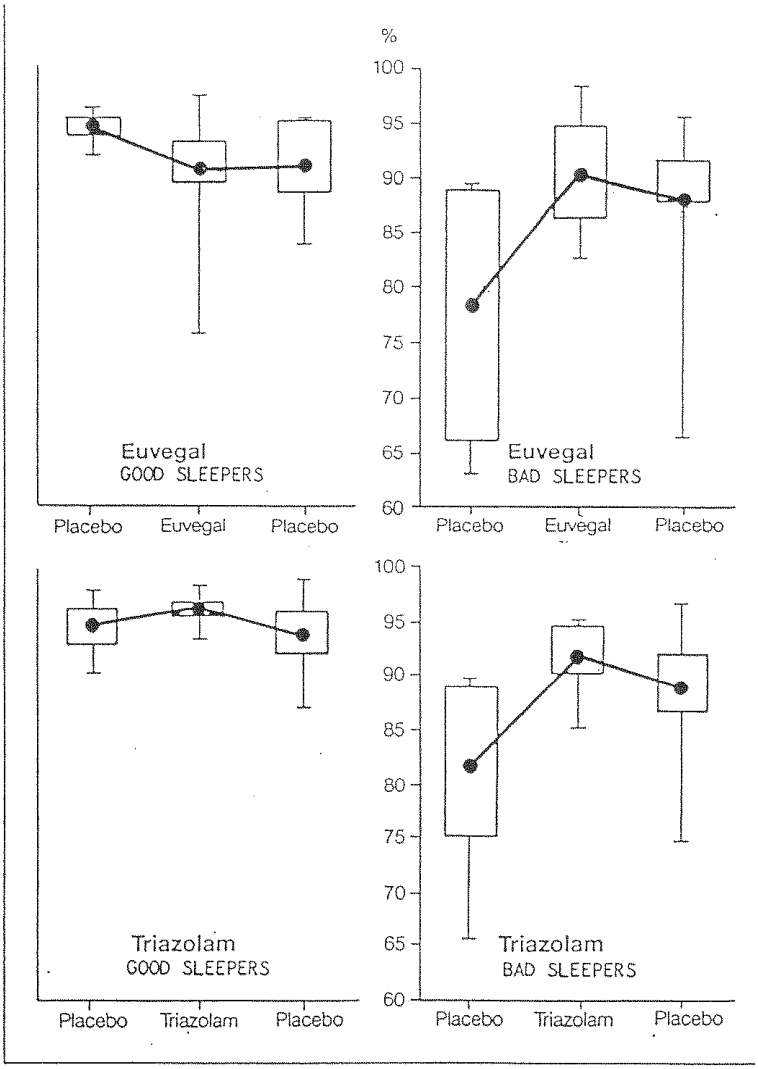
Concentration and performance were not restricted

Contrary to many synthetically manufactured preparations, the valerian/balm preparation also did not have any influence on the concentration and performance of the participants. Thus, after treatment with the valerian/balm preparation, the authors wer not able to establish any restriction in their concentration and performance by comparison with placebo, either in the the concentration and performance test or in the labyrinth test carried out. In fact, the actively treated group even had better, i.e. above-random results than the placebo group where the parameters »error percentage« and »error quotient« were concerned.

The demonstrated increase of deep sleep stages in the group of bad sleepers is a remarkable test result and is representative for the positive effect of the valerian/balm preparation.

Over and beyond this, the absence of a rebound effect and the absence of a daytime sedation effect after the nighttime intake of the valerian/balm preparation are to be emphasized as positive results of this study.

Fig. 4: Sleep efficiency in percentage of time in bed



Conclusion: the sleep-improving effect of the valerian/balm preparation is demonstrated

The results here obtained demonstrate that plant-based combination preparations such as high-dosage valerian/balm combinations present a thoroughly effective and safe alternative to benzodiazepines in the treatment of specific sleeping disturbances (e.g. psychoautonomically conditioned or psychosomatic disorders in the initial and maintained sleep phases). In further studies, therefore, it must be investigated whether the sleep-improving effect of the valerian/balm preparation subjected to investigation in this study can also be established in a clinical population of patients suffering from sleep disorders and whether these effects remain demonstrable over periods of investigation lasting for a number of weeks or more.

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SUMMARY

In general practice, the treatment of insomnia is a domaine of the benzodiazepines. Long-term treatment with benzodiazepines, however, may lead to a number of risks and unwanted side-effects. These risks justify the search for alternative forms of therapy in the treatment of sleep disorders. Although today the use of valerian preparations has become widespread, only a limited number of studies have been carried out in which the therapeutic application of valerian preparations has been the subject of thorough scientific investigation.

This study is aimed at testing the effects of a new valerian preparation on the sleep of healthy volunteers. The median values of sleep efficiency of the volunteers represented the criteria for the formation of 2 groups into good and poor sleepers. The use of the valerian preparation on the group of poor sleepers induced a significant increase in sleep efficiency and in sleep stages 3 and 4. The statistically significant increase in delta sleep in the group of poor sleepers constitutes an interesting result which did not occur in comparable investigations. Rebound effects were not observed, either for the valerian preparation or for Triazolam.

RECOMMENDED IN PRACTICE

The application of plant-based sedatives should be considered as a method of first choice in patients:

- whose sleep disturbances are not caused by external influences (e.g. noise or light) or produced by organic conditions (e.g. pain)
- in whom sleep disturbances require treatment for the first time
- who suffer from psychoautonomically conditioned or psychosomatic disorders
- who are victims of mild to moderately severe diseases
- in whom no powerful sedation is needed within a short time, and
- who are not restricted or even endangered by the side-effects of chemical psychopharmaceuticals.

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