Treatment of sleep disturbances
in general practice
(W. Weyers/P. Periat)

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Sleep disturbances, irritability and restlessness are widespread disorders in modern industrial societies, presumably caused by exogenous, physical overstimulation. Between 20 and 25% of all patients treated in general practice complain of sleep disturbances [1, 2] and in psychiatric clinics this percentage increases as far as about 70%. So it is hardly surprising that some 5% of all drugs prescribed are soporifics or sedatives [2].

The range of "hypnotic and sedative agents" available to the doctor for the treatment of relevant health disorders, symptoms or diseases is correspondingly large [3]: benzodiazepine hypnotics, non-benzodiazepine hypnotics (e.g. chloral hydrate, barbiturates), other chemically defined sedatives (e.g. antihistamines), newer substances, which act on the benzodiazepine receptors (e.g. zolpidem, zopiclone) and natural preparations (e.g. phytopharmaceuticals, alcohol, DSIP).

Only a detailed diagnosis can reveal whether drugs need to be used at all in the case of sleep disturbances. Many sleep disturbances are the result of organic diseases and should thus be treated by treating the cause. Other disturbances may be caused by psychoses within the manic-depressive group and need to be treated with specific psychopharmaceutical agents. But there can be no doubt that a considerable number of the sleep disturbances reported by patients in general practice can be classed in the field of general health disorders or mild symptoms. The patient usually greatly overestimates the average physiological period of sleep (Table 1).
The doctor must therefore adapt his treatment according to the principle "primum nil nocere" to the severity of the disturbance. In this context, phytopharmaceuticals, as "mite" (mild) drugs, will probably be sufficient as an initial treatment for many patients, since the possibility of a transition to stronger drugs still remains. The report below is of an open, multicentric study carried out as long ago as 1978 on 179 patients and re-evaluated here, together with a report of an open, controlled study carried out in 1990 on 30 patients. Both studies were carried out in Switzerland.

Table 1. Average physiological duration of sleep:

<table>
<thead>
<tr>
<th>Age</th>
<th>Hours:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>16</td>
</tr>
<tr>
<td>2 to 3 years old</td>
<td>12</td>
</tr>
<tr>
<td>10 to 14 years old</td>
<td>10</td>
</tr>
<tr>
<td>14 to 18 years old</td>
<td>8.5</td>
</tr>
<tr>
<td>Adults up to 70 years old</td>
<td>6 - 9</td>
</tr>
<tr>
<td>Over 70 years old</td>
<td>5.5 - 6</td>
</tr>
</tbody>
</table>

Basic principles

The trial of and collection of therapeutic experience with respect to phytopharmaceuticals continues to meet with major problems in practice. Many phytopharmaceuticals are purchased and used by the patients as self-medication so that critical evaluation of therapeutic success is not possible.

Placebo-controlled studies are frequently not possible, since preparations of this type - this applies in particular to the product Bio-Strath Sedative Formula No 8*) used here, which contains valerian - have an intense intrinsic odour and taste which cannot be sufficiently well imitated in a placebo to prevent the patients distinguishing between placebo and active treatment. On the other hand, a comparative study between a

*) a product of Bio-Strath AG, CH-8032 Zurich
plant-based "mite" drug and hypnotics or sedatives and tranquilisers is also ruled out.

The qualities of action of the benzodiazepines, for example, and the strengths of the action of, say, the barbiturates are so different from those of the plant extracts of valerian, passionflower and peppermint used here that even if the dosages were approximately aligned, only a scientifically inadmissible comparison could be drawn [4]. For instance, no hypnotic effect can be demonstrated with valerian even at extremely high doses [5], however there is an increase in amplitude of the amygdalo-hippocampal responses, suggesting a thymoleptic action. Thus, in general, sleep cannot be enforced with either valerian or passionflower extract, but readiness for sleep can be encouraged.

This left the implementation of open studies as the only alternative. The unavoidable subjective nature of the assessment of personal condition by the patient and the fact that, particularly in the field of indications "sleep disturbances" and "sleep disturbances with neurovegetative dystonia", the assessment by the doctor is based principally on the doctor's case notes and is thus also subjective, can be mitigated only by the fact of a fairly large patient population, the multicentric structure of a study of this type and/or controls based on psychological assessment scales.

Method
Open, multicentric study

179 patients were included in this study and assessed four times each by 35 doctors (5.1 patients per doctor) during the four-week study. They also assessed themselves four times each. This means that a total of 10 assessments of efficacy and tolerability were available for each patient, permitting a scientifically useful statement to be made on the basis of this open study.
The duration of the investigation was 4 weeks. Patient and doctor each completed a separate questionnaire at each consultation, the questionnaires containing questions on general health in addition to those regarding efficacy and tolerability.

As a further check, the questionnaires also contained a question as to the effect on "sweating", such an effect being unlikely with the drug tested. At the initial examination, data were recorded regarding other drugs used, fitness for work, physical activity and recommended diet, in addition to the diagnosis.

Subsequent evaluation of the doctor/patient forms [6]: 11 of the 179 doctor and patient forms were initially excluded from the evaluation because the patients had discontinued the treatment (5 cases) or because concomitant diseases had occurred in the meantime. 28 patient questionnaires were not evaluated because 21 patients had received additional treatment which might have influenced the results of this study and because insomnia or nervous complaints had not been central in the case history when the doctor was consulted in the case of 7 patients.

After these strict exclusion criteria for an open, multicentric study with 35 doctors, 140 patients remained for evaluation. 75% of these were female and 25% male. Evaluation was undertaken on the basis of the "efficacy" criterion after the 1st, 2nd, 3rd and 4th weeks of treatment and on the basis of the "tolerability" criterion after the 4th week of treatment, using a 5-step scale in each case: -2 = very poor; -1 = poor; 0 = no clear/no observation; +1 = good; +2 = very good. The results were separated according to data from the doctor and the patient in each case.

(4)
Open, controlled study

Data were recorded when the 30 patients were examined for inclusion in the study and after completion of the treatment, an average of 24 days. The clinical assessment of efficacy and tolerability of the test substance by the doctor treating the patient and by the patients themselves was undertaken after completion of the treatment using a four-step scale: "very good", "good", "moderate", "poor".

Since objectification of the assessment was absolutely essential, particularly in the case of the underlying clinical syndrome in this trial, "Zerssen's List of Symptoms" was used both before and after completion of the treatment. This is a clinical self-assessment scale, the reliability and validity of which has been proved in numerous studies for measuring somatic symptoms in cases of mental disorders [7, 8, 9]. The patients are given a list of symptoms, such as "lack of appetite, stabbing pains, aches or pulling pains in the chest, low back pain or backache," etc. only a small number of which are linked to the health disorder or disease being treated. The patients mark their present condition using a four-step scale (severe, moderate, hardly any, none). In order to avoid systematic disturbance effects (e.g. learned effects), the two half-forms (BL and BL') of the List of Symptoms were used, containing 24 questions each. The scale values of the two half-forms correlate with one another to such a high degree ($r = 0.8$) that comparable results are provided in the case of psychovegetative and somatic symptoms in mental disturbances even though the two half-forms contain questions about very different symptoms. Alternating systematically, the patients (every second patient, $n = 14$) completed half-form BL for the "before" assessment and half-form BL' for the "after" assessment or vice versa (the other patients, $n = 14$). Two patients were excluded from the evaluation because benzodiazepines had had to be given in addition to the test substance.
Patient population

The selection of patients was left to the test physicians treating them. Cooperative patients with sleep disturbances and sleep disturbances with neurovegetative dystonia took part in the study. Patients with serious concomitant diseases were excluded, together with patients who were taking psychopharmaceuticals and/or soporifics, who did not attend for the intermediate and/or final examinations and for whom it could not be guaranteed that the test substance would be taken regularly.

Of the 179 patients originally included in the multicentric study, 8% were children aged up to 14 years, 70% were of an age to be receiving education or training or to be working, i.e. between 15 and 59 years and 22% were of pensionable age, i.e. over 60. 77% of the patients were female, 23% male. The mean age of the 30 patients in the controlled study was 46.2 years (s = 15.6 years). 20 patients had difficulties falling asleep, 9 had problems with sleeping through the night. Another 9 patients consulted the doctor for general nervousness in connection with the sleep disturbances already mentioned. 57% of the patients were female, 43% male.

Test preparation/dose

According to the manufacturers' declaration, 100 ml of the test preparation, Bio-Strath Sedative Formula No. 8, contains 22.5 ml Extr. Rhiz. Valerianae off., 22.5 ml Extr. Herb. Passiflorae inc. and 5.0 ml Extr. Fol. Menthae pip. in a yeast plasmolysate base.

The preparation has weak thymoleptic, anticonvulsive, spasmolytic and sedative properties and has been shown in preclinical trials to be virtually nontoxic and free of side effects [17, 18]. The alcohol content of the preparation is only 30% by volume so that the influence of alcohol on the action of the preparation can be ruled out at the prescribed dose of 20
drops 3 times daily. This dose was complied with by 73% of the patients suitable for evaluation in the multicentric study. The dose was reduced by 17% of the patients, generally to 20 drops once a day in the evenings. In the case of 10% of the patients it was increased to 30 to 40 drops 3 times daily.

In the controlled study, the doses were prescribed individually, the drops generally being taken in the evenings. The average dose was 33 drops per day (20 drops once to 20 drops three times daily), which was on average considerably lower than in the multicentric study.

The mean duration of the symptoms classed by the doctor as mild to moderately severe was 12.7 months prior to the start of the study.

Results
Open, multicentric study

Efficacy: The total of 463 scores evaluated from the doctor's data yields a mean value of +0.856, corresponding in total to just below a "good" assessment of efficacy.

If we look at the efficacy curve, it can be seen that the doctors assessed efficacy as very good after only one week of treatment in only 5.0% of the patients, but that this percentage increased to 34.28% in the course of the four weeks of treatment. The total of 501 scores evaluated from the patients' data yields a mean value of +0.845, again corresponding in total to just below a "good" assessment of efficacy. 5.71% of the patients described the efficacy as very good after one week of treatment, but this percentage increased in the course of the four weeks of treatment to 19.2%.

This influence of duration of therapy on therapy success can also be seen clearly in the cases of therapy failure. After one week of treatment the success of the treatment ranged from
"very poor" to "no clear effect" according to the doctors' data for 32.8% of the patients (patients' data: 32.1%). This percentage drops to 15.7% (doctors' data) and 18.6% (patients' data) over the four weeks of treatment (Fig. 1).

![Diagram](image)

**Figure 1. Assessment of therapy success by the doctors as a function of duration of therapy in the case of 140 patients**

The mean value for tolerability is assessed as +1.03 by 139 patients and as 1.0 by the doctors, i.e. uniformly as good. In only 5 cases (= 3.57%) do the doctors report intolerance. There are no more precise details in this context but the patients' record sheets show that this is associated with the apparently unpleasant taste of the test preparation and thus refers to gastric intolerance phenomena.

The "sweating" criterion was not affected by the test preparation and nor was appetite. On the other hand, the patients reported an increase in powers of concentration, which is
likely to be directly linked to the efficacy in combating sleep disturbances.

**Controlled, open study**

Both doctor (43.4%) and patients (44.5%) assessed therapy success as good to very good. It was assessed as moderate in 40.7% and 37.0% of cases respectively and as poor in only 7.5% and 11.1% of cases. Hence, surprisingly, the results lie within the same framework as those of the multicentric study which was carried out far earlier and by other test doctors.

Tolerability was assessed by 89% of the patients as good to very good. One female patient (3.6%) aged 62 years, noted pruritus some 1 hour after taking the preparation but this did not cause her to discontinue the treatment. However, this patient was being treated simultaneously with drugs to combat hypertension.

In 82% of cases the symptoms had improved or the patients were almost free of symptoms by the end of the three-week study (Table 2). In 18% of cases there was no change. This overall evaluation is confirmed by the results of the statistical analysis of "Zerssen's List of Symptoms".

The one-tailed hypothesis that "The scale values of the "after" measurement are on average lower than those of the "before" measurement" was tested for non-independent samples using Student's t-test. The t-value calculated of 2.19 (df = 28) is significant (t = less than 0.05). However, this statement is adversely affected by the small sample size of 28. We can assume that greater significance could be achieved with a larger sample size. The mean effect size according to Cohen [10] could be determined as being large, proving the efficacy of the preparation used.
Table 2. Change in symptoms (n = 28):

- Free of symptoms      0%
- Almost free of symptoms 21%
- Improved              61%
- Unchanged             18%
- Deteriorated          0%

Discussion

During the three to four-week treatment of mild to moderately severe sleep disturbances with the test preparation in a total of 168 patients suitable for evaluation, two studies implemented independently of one another in general practices in Switzerland demonstrated a clear improvement of symptoms in more than 80% of patients, although the sleep disturbances had been present for a fairly long time prior to the patients consulting a doctor for treatment. The assessment by the doctors differed only insignificantly from that by the patients. This result is confirmed by the statistically significant difference between the "before" and "after" measurements using "Zerssen's List of Symptoms". The increase in therapy success with duration of treatment demonstrated in the multicentric study is particularly worthy of note.

Despite the controls built into the multicentric studies and the control based on "Zerssen's List of Symptoms", the studies were unable to provide an answer to the questions of spontaneous remission rate and placebo effect which are particularly high in the case of sleep-promoting and sedative agents [11, 12, 13].

Although the test doctors did not devote more attention to the patients participating in the study than to their other patients, the possibility that simply completing the report forms had a positive influence on the therapy cannot be ruled out. However, this effect should not be overestimated either, particularly in the area of indications being investigated here, as has been expressly pointed out by Rickels [14].
thermore, as mentioned at the start of this paper, every attempt was made to keep this effect to a minimum by using as large a patient population as possible (168) and a fairly large number of investigators (36).

As has already been mentioned, it is not possible to undertake a placebo-controlled double-blind study because of the specific odour of valerian in the test preparation and a controlled, double-blind study of hypnotics/sedatives is not scientifically admissible [4]. Mention should certainly be made of the work of Helmchen [16], which proves that double-blind studies by no means always provide more correct or more precise results than studies which are well planned and open but controlled.

Although, as has already been mentioned, it is not strictly admissible, a comparison of the "mite" phytotherapeutic agent tested here with benzodiazepine preparations should still be investigated in a few cases. In five cases in the controlled, open study, the patients were unable to do without the benzodiazepine preparations previously (although not regularly) used for their symptoms. However, at the same time, the limits of "mite" phytotherapy of this type are also demonstrated: in the case of two patients with pronounced habituation to benzodiazepines, these could not be replaced by the test preparation. The sample size for a Phase III study with 168 patients evaluated was sufficiently large for a significant statement to be made [15].

Thus, it was possible to demonstrate overall that in the case of mild to moderately severe sleep disturbances, such as are reported by between 20 and 25% of all patients in general practice, treatment with a "mite" phytopharmaceutical agent, such as Bio-Strath Sedative Formula No. 8, tested here, is entirely adequate. Furthermore, the test preparation is virtually nontoxic [17], almost free of side effects, non-addictive and has no withdrawal problems at all. It thus meets the
requirements of sleep physiologists who nowadays prefer drugs which encourage readiness for sleep to those which enforce sleep. The chemically defined sedatives, hypnotic agents and psychopharmaceuticals mentioned above can then be reserved for severe sleep disturbances.

References

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