to determine what percentage of the individuals who report trouble with sleeping have or
do not have accompanying mental or physical pathologies.
In response to your second question, I have mentioned that some of our patients
seem to derive benefit from sleeping in the laboratory, but others do not. We do not yet
know the significance of these differential response patterns. We hope that study of
patients in their homes, with less conspicuous machinery and over a long enough time for
the novelty to disappear, will help us explain this phenomenon.
Sleep : Physiology, Biochemistry, Psychology, Pharmacology, Clinical Implications.

Some Problems of the Therapy of Sleep Disturbances
in Depressed Patients

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Sleep disturbances in depressed patients are among the leading symptoms
which have lately attracted the attention of many research scientists
in the field of clinical psychiatry [Hajnsek et al., in press; Hawkins and
Mendels, 1966; Hinton, 1963; Toyoda, 1964; Willis, 1965; Zung, 1969,
1970], The therapy of these disturbances still presents a great problem, and
the therapeutic approaches are often contradictory.
Research workers in this field are primarily interested in discovering
whether there is any correlation between the course of sleep and the clinical
symptoms. It depends upon the research worker which drug will be applied
and how its effect will be assessed [Dürrigl et al, in press; Jovanovic,
1972c, h; Jovanovic et al, 1972a].
We examined the sleep of depressive patients by using the polygraphic
technique (in collaboration with Dr. Jovanovič, Würzburg). We were
interested to learn how anti-depressants such as imipramine and maprotiline
affected these disturbances. Since previous clinical examinations
showed a positive effect of these preparations [Dürrigl et al., in press;
Hajnsek et al., in press; Jovanovič, 1972c; Jovanovič et al., 1972a], which
nevertheless seem to differ from each other, we decided to test the preparations
by means of the polygraphic technique, bearing in mind that the
neurophysiological tests with a simultaneous examination of a series of
parameters would yield better and more precise results.
The findings reported relate to 20 patients suffering from endogenous depression whom we treated for 25 days. The patients were randomly divided into two groups. 10 patients received maprotiline and the other 10 received imipramine. The first part of the trial lasted 10 days. The patients were given placebo for the first 3 days, active substance for the next 5, and placebo again for the last 2 days. All were tested clinically and polygraphically for these 10 days. In the second part of the trial, lasting 15 days, only active substance was administered. The sleep patterns of each patient were again polygraphically recorded for the last 5 nights of this period; clinical examinations only were performed for a further 10-day period (table III).
The following tests were carried out: EEG, EOG, EMG, ECG and direct observations. The results of clinical examinations and answers to special questionnaires were also taken into account in the assessment of these cases. The polygraphic records obtained in this group thus covered 300 nights.

Fig. 3. Distribution of sleep stages in depressive patients.

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Table III. Plan of treatment and dosage used

Using visual examination the following parameters were taken into consideration: (1) the assessment of sleep stages (scoring each minute); (2) rapid eye movements (upwards, downwards, to the right, to the left, predominantly downwards, etc.); (3) motor activity during sleep, i.e. turning in bed with or without waking up, change of position in bed without turning over and with or without waking up, body movements involving no change in position in bed, coarse limb movements, fine movements and twitching of the limbs; (4) heart rate, and (5) answers to completed questionnaires on the test subjects’ mood before and after sleep.
We shall refer here only to those of our results which already have been statistically processed, e.g.: (1) the depth of sleep; (2) number and duration of waking periods; (3) sleep periodicity; (4) motor activity, and (5) some autonomic functions such as, for instance, the heart rate.
The total duration of sleep in this group of depressed patients was about the same before and after treatment with maprotiline and imipramine. This parameter, however, is of no great value because it does not show whether the patients slept continuously or not. It is, therefore, more informative to examine the distribution of the various stages of sleep (fig. 3).
Prior to the administration of maprotiline, the waking stage was longer in the depressed patients than in the normal subjects, amounting in fact to almost 2 h. During 5-day treatment with maprotiline, the total duration of waking episodes fell from almost 2 h to less than 1 h. In turn, imipramine administered in the same dosage prolonged the waking stage. Following the withdrawal of maprotiline, the total duration of waking episodes increased again, but without attaining the figure recorded prior to treatment with the drug. In the depressive patients stage A was relatively short before treatment and was even a little further reduced by both drugs. Stage B, before treatment, was likewise somewhat shorter in the depressive patients than in normal subjects; in response to maprotiline, it increased and reached the same percentage figure as in normal subjects, whereas in response to imipramine it tended to become even further reduced. Stage C, before treatment, was just as long in depressive patients as in normal subjects. Its duration increased a little in response to maprotiline, while it somewhat decreased in response to imipramine. Stage D in the depressive patients was at the lower limit of the normal range prior to treatment. Its duration decreased still further, though not significantly in response to maprotiline, whereas it increased in response to imipramine. Following the withdrawal of maprotiline, the duration of stage D tended to increase. Both drugs reduced the duration of stage E. The REM phases were extremely short in the depressive patients prior to treatment. During medication with maprotiline, their duration returned to almost normal, whereas they became even shorter in response to imipramine. Following the withdrawal of maprotiline, the duration of the dream phases decreased again, but only to a slight extent. After a treatment of 25 days, sleep in the depressive patients returned to normal. There were no longer differences to be seen in the effects of maprotiline and imipramine. Of particular interest are the findings concerning the duration of the waking episodes. When not receiving any treatment, the depressive patients stayed awake for long periods during the night - for much longer, in fact, than normal subjects. The phases of deep sleep were represented by only a small percentage. They needed a long time to fall asleep and woke up often; evidently the regulation of the sleeping periods was disturbed. During the
first 5 days of the treatment, maprotiline reduced both the total duration of waking episodes and the duration of waking episodes in each of the various stages. Imipramine, in turn, prolonged wakefulness during the night. It is a well-known fact that, in patients suffering from depression, sleep is particularly likely to be disturbed after midnight and towards morning. In the present study, too, this phenomenon clearly became apparent when we analyzed the duration of the various periods or cycles of sleep (P) in the course of the night.

Prior to treatment, sleep period I (Pr) was extremely long in the depressive patients. During the first 5 days under medication with maprotiline, it was considerably reduced. After the treatment with imipramine, it became longer. Sleep period II (Pn), before treatment, was somewhat shorter in depressive patients as compared to normal subjects. During treatment with maprotiline, it became longer. Sleep period III (Pm), likewise increased in response to maprotiline - from 61.778 to 73.687 min. Sleep period IV (PIV),

Fig. 5. Motor activity of depressive patients before treatment.

which was very short prior to treatment, also increased from 34.411 to 75.474 min during treatment with maprotiline, but did not attain the duration observed in normal subjects. The effects of imipramine differed from those of maprotiline in all sleep periods (fig. 4). An essential difference between maprotiline and imipramine was found in their effects on sleep periodicity in depressive patients during the first 5 days of the treatment. Maprotiline lengthened the short periods of sleep after midnight and shortened the long periods immediately after the onset of sleep, to render sleep periodicity as a whole similar, or nearly similar, to those of normal subjects.

Hence, sleep disturbances occurring after midnight and towards morning in the depressive patients were improved or even eliminated, which presents a finding of considerable clinical importance. In response to imipramine, the depressive patients slept mainly during the first few hours, even after 5 days of treatment with the drug. But their sleep periodicity still did not return to the normal level.

When analyzing the motor activity in the depressive patients (statistical elaboration was done for only 9 patients), it was obvious that the depressive patients were mostly disturbed before going to sleep and after midnight (fig. 5). Following the fifth day of treatment with maprotiline, the intensity of motor activity was decreased and sleep periods improved (in the middle of figure 6 one can see a smaller number of movements because the patients were asleep). Before treatment they were awake at that time (cf. fig. 5, 6).
Following the fifth day of treatment with imipramine, although the motor activity was slightly diminished, the sleep cycles were practically unchanged (fig. 7). After a treatment of 25 days the effects of the two substances were about the same.

Fig. 6. Motor activity of depressive patients following the fifth day of treatment with maprotiline.

Fig. 7. Motor activity of depressive patients following the fifth day of treatment with imipramine.

WICKSTRÖM Clinical Trial of Flurazepam

Summary

1. The various clinical types of endogenous depression, where insomnia is a dominant symptom, can be successfully treated with drugs other than hypnotics - as can be seen from this trial with two thymoleptic drugs.
2. In the course of treatment, maprotiline and imipramine differed from each other as to their effects on the depth of sleep, but at the end of a therapy of 25 days, the effects were about equal. The positive effect of maprotiline appeared earlier than that of imipramine.
3. In the course of the treatment, the normalization of the cycles of sleep showed differences, too. At the end of a therapy of 25 days, there were no longer any differences.
4. The same was observed for the motor activity during sleep.
5. During the treatment with imipramine, the heart rate was much higher than before and after the therapy. Under maprotiline the heart rate did not change very much. At the end of the treatment, no differences could be ascertained.
6. Our findings suggest that patience is needed when one treats sleep disturbances: one cannot stop the treatment with a pharmacological agent after only 3 days simply because the drug does not produce satisfactory effects at once.

Flurazepam is a new hypnotic of the benzodiazepine type. It is a yellow, crystalline substance which is soluble in water and in alcohol. Results from animal studies indicate that flurazepam has the anti-convulsant, sedative and muscle-relaxant properties which are common to other compounds of this group. Clinical trials have shown that flurazepam shows a good hypnotic effect when given at a dose of 30 mg [Randal et al., 1969]. A series of sleep investigations with flurazepam (including EEG, EMG and EOG studies) has been carried out in the USA [Kales et al., 1969]. Flura-

4 F. Hoffmann-La Roche: 7-Chloro-1-[2-(diethylamino)ethyl]-5-(o-fluorophenyl)-1,3dihydro-2H-1,4-benzodiazepin-2-one dihydrochloride (=Dalmadorm®, =Dalmane® [USA]).