186-191 *Clinical rheumatology*, 1993, **12**, N° 2

Effect of Zopiclone on Sleep Quality, Morning Stiffness, Widespread Tenderness and Pain and General Discomfort in Primary Fibromyalgia Patients. A Double-Blind Randomized Trial

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Summary **Thirty-three patients fulfilling the diagnostic criteria for primary fibromyalgia completed an eight-week double-blind treatment trial with the drug zopiclone. Of outcome measures studied a score expressing subjective sleep quality showed improvement in more than ninety percent of zopiclone patients at 4 weeks and nearly eighty percent at 8 weeks, but similar improvement was also reported by more than sixty percent of the patients on placebo. Patient self-assessment of a treatment effect also showed an advantage for zopiclone, with most patients in the placebo group considering their state as unchanged at 8 weeks. According to examiner assessment, however, half the patients in both groups showed improvement at 8 weeks. For other assessment variables, e.g. dolorimeter assessment of widespread tenderness, visual analogue scales and pain drawings for pain and other subjective feelings of discomfort, the effects of zopiclone treatment were at the same level as those of placebo.**

INTRODUCTION

Sleep disturbance is common in, but not specific for, the chronic widespread musculoskeletal pain condition designated as primary fibromyalgia (1-3). It is not, however, included in the more recent diagnostic criteria for fibromyalgia by the American College of Rheumatology (3). In that study sleep disturbance was present in 75.6% of patients designated to have primary fibromyalgia, whereas 31.1% of controls had such complaints.

Zopiclone has a reported advantageous effect on sleep, with a specific increase of stage 3 sleep (4) and in a recent study on fibromyalgia patients subjective sleep quality was improved, awakenings during the night were reduced in number ($p<.05$) and there was less tiredness in the daytime ($p<.05$) (5).

In the present study the effect of zopiclone (7.5 mg) and placebo were compared in an 8-week double-blind trial. Widespread tenderness and pain were assessed with a pressure pain score obtained with a dolorimeter, sum scores of visual analogue scales depicting various body areas and pain drawings. Special emphasis was placed on the assessment of widespread pain and tenderness, since these are considered most important in fibromyalgia (3,6). A subjective global sleep score, a sum score for duration and severity of morning stiffness, an assessment of subjective improvement by the patient and examiner assessment of improvement were used as additional outcome measures.

SUBJECTS AND METHODS

Patients and study protocol

Forty-nine consecutive patients fulfilling the diagnostic criteria for primary fibromyalgia of Yunus et al. (2) were considered eligible for the study. All patients entering the study signed a written consent and the study was approved by the hospital ethical committee and the National Medical Board. Patients experiencing side-effects during the course of the study were allowed to drop out after consulting with one of the investigators. No escape medication was permitted. Their median age was 45 years (range 17-67 years) and they had had widespread pain symptoms for (median, quartiles) 4.5 years

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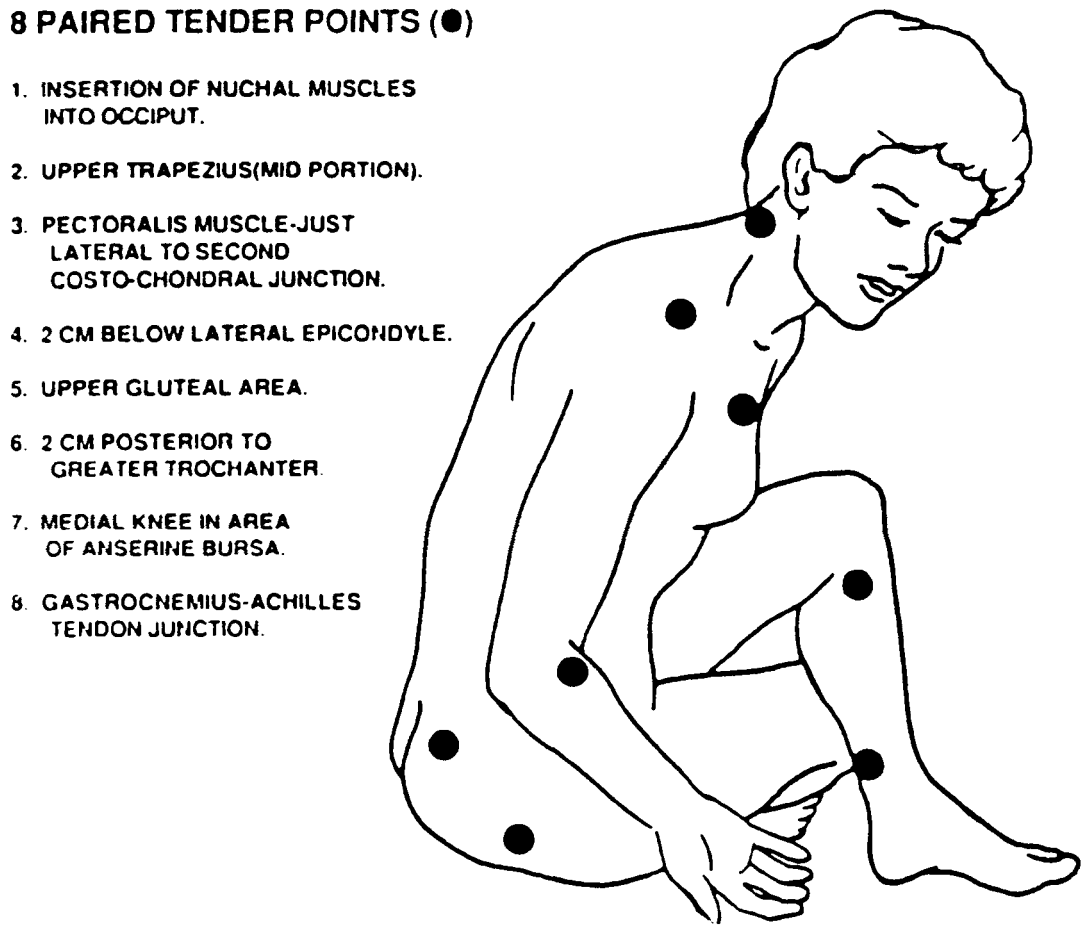

Fig. 1: Pressure pain threshold was measured bilaterally at eight typical fibromyalgia tender areas with a dolorimeter.

(2, 10 years). None of the patients had any major disease explaining their symptoms. They had all been thoroughly examined clinically by a rheumatologist to exclude other rheumatic diseases, had normal laboratory reports and X-rays taken prior to referral showed low-grade osteoarthritis at most. During the course of the study no other analgesic, psychiatric or sleep medication was allowed. The patients were randomized by an uninvolved third party into a group receiving zopiclone (7.5 mg every evening for a total of 8 weeks; 24 patients) and a group receiving placebo (25 patients).

Three patients (two in the zopiclone group, one in the placebo group) decided not to participate in the study after all, before taking any medication. Two patients taking placebo medication had to be excluded, one because of concomitant medication and the other because she could not follow the time table of appointments. One patient taking zopiclone dropped out before her second appointment without reporting any specific reason. Three patients taking placebo and seven taking zopiclone experienced what they interpreted to be drug side-effects and were permitted to drop out according to the agreement made when entering the study. None of the side-effects were serious. Excluded patients showed no clear differences compared to the included patients with respect to sex and age distribution, duration of pain and percentage of patients working. Baseline scores for all patients, including those not completing the study, were plotted separately for every assessment variable and the distribution of the scores of these patients was found not to be skewed in comparison with the scores of those completing the study.

A total of 33 patients (19 in placebo group, 14 in zopiclone group; 67 percent of all patients found eligible) completed the study. All patients in the placebo group were women, in the zopiclone group two were men. In the placebo group thirteen (68%) were doing their regular work, whereas in the zopiclone group ten (71%) were doing their regular work. The median ages of the placebo and zopiclone groups were 43 years (range 26-67 years) and 48.5 years (range 17-57 years) respectively. They had had widespread pain for (medi-

Table I: *Estimate of variance for repeated measurements (s^2) with the dolorimeter at fibromyalgia tender areas in twelve patients (p = number of measurement pairs)*

Level	1.0-1.9		2.0-2.9		3.0-3.9		4.0-11	
(kg/1.54 cm^2)	s^2	p	s^2	p	s^2	p	s^2	p
	0.12	80	0.35	76	0.65	33	*	

*s^2 not calculated because of low number of measurement pairs.

an, quartiles) 5 years (2, 11 years) and 4 years (1, 5 years) respectively. Patients were examined by a rheumatologist and then completed a structured patient interview. Patients met with the examiner at 0, 4 and 8 weeks, each time completing a patient questionnaire. At each patient visit, the examiner also assessed pressure pain threshold using a 1.54 cm^2 flat-disc dolorimeter (7) at eight bilateral typical fibromyalgia body areas (2, 3) (Fig. 1).

Matching of groups

Placebo and zopiclone groups were matched with respect to baseline global sleep scores, since the treatment effect was found to be most marked with respect to this assessment variable. The comparison groups thus obtained were then used for all the other treatment assessment variables as well. At baseline, the groups were matched by ranking sleep scores for all subjects and then forming as equal as possible mean ranks for the groups in common ranking. This resulted in the exclusion of five subjects (numbers 10, 14, 17, 38 and 45) from the placebo group, leaving 14 patients in both groups.

Assessments

Blinded to the treatment, the examiner and the patient separately assessed the effect of treatment at 4 weeks and 8 weeks, using a 1-6 graded scale (range: definitely worse to fully recovered). Possible side-effects from drug treatment were assessed at 4 weeks and 8 weeks, grading the observed effect as mild, severe and very severe. Sleep disturbance was assessed by the patient, separately for falling asleep (scale 0-4), sleep quality (scale 0-4), length of sleep (scale 0-2), number of awakenings during night (scale 0-3), feeling energetic in the morning (restorative sleep; scale 0-4). A global sleep quality score was then obtained. The duration and intensity of morning stiffness was assessed at 0, 4 and 8 weeks (average during preceding week). Duration was graded as 0 = less than or equal to 15 minutes, 1 = maximum one hour and 2 = more than one hour. The duration score was added to a score (scale 1-5) expressing intensity, giving a global score expressing a combination of duration and intensity of morning stiffness. Aching was assessed with four 100 mm visual analogue scales (VAS) (8), one for the upper and one for the lower extremities and one for the upper and one for the lower torso. The body areas implicated were carefully explained to the patient. A VAS score for the entire body was thus obtained. Sharp pain, numbness, fatigue or stiffness were similarly assessed. Since multiple visual analogue scales were used, the obtained raw VAS scores were for simplification transformed to scores of 0, 0.5 or 1. Thus a maximum VAS score of 16 could be obtained for widespread combined pain (aching and sharp pain) and numbness, fatigue and stiffness. Similarly, a maximum score of 8 could be obtained for pain only (aching and sharp pain combined).

The above-mentioned pain qualities were also assessed using four pain drawings, where all the body areas involved, including areas of referred pain, were carefully marked by the patient using a standard-size mark as a model. A transparent templet of 5 × 5 mm squares was then placed over the pain drawings and the number of squares containing whole marks or with marks crossing their borders were counted (9). Scores were then summed up to give a global score of pain distribution. Thus aching, sharp pain, numbness and fatigue or stiffness in the entire body were assessed with both VAS:s and pain drawings. To simplify the process obtained, pain drawing scores were counted as the value closest to ten and a global pain drawing score expressing all subjective feelings (pain and others combined); a score for pain only (aching and sharp pain combined) was assessed separately.

For outcome assessment the number and percentage of patients improved, unchanged or worse with respect to every variable were compared for placebo and zopiclone groups.

Dolorimeter measurement

The repeatability of dolorimeter measurement was examined in twelve of the patients. It was expressed as the estimate of variance and was analyzed at different levels of pressure pain threshold. Measurement was repeated at the eight bilateral fibromyalgia tender areas with a time interval of 30 minutes.

RESULTS

Repeatability of dolorimeter measurement in fibromyalgia patients

Only one examiner carried out all dolorimeter measurements. Repeated measurement resulted in a mod-

Table II: *Fibromyalgia patients improved, unchanged or worsened at 4 weeks and 8 weeks according to patient self-assessment and examiner assessment**

	Improved	Unchanged	Worsened	Total
Self-assessment:				
at 4 weeks:				
Placebo	5	7	2	14
Zopiclone	8	4	2	14
at 8 weeks:				
Placebo	4	8	2	14
Zopiclone	6	3	5	14
Examiner assessment:				
at 4 weeks:				
Placebo	3	11	0	14
Zopiclone	4	9	1	14
at 8 weeks:				
Placebo	7	6	1	14
Zopiclone	7	6	1	14

*Scale 1-6 (from definitely worse = 1 to fully recovered = 6). Patient groups in this table and all subsequent tables have been matched at baseline (see Subjects and Methods).

Table III: *Fibromyalgia patients with better, unchanged or worsened global sleep score and subjective morning stiffness at 4 and 8 weeks*

	Better	Unchanged	Worsened	Total
Sleep score:				
at 4 weeks:				
Placebo	9	3	2	14
Zopiclone	13	0	1	14
at 8 weeks:				
Placebo	9	3	2	14
Zopiclone	11	2	1	14
Morning stiffness:				
at 4 weeks:				
Placebo	5	6	3	14
Zopiclone	6	5	3	14
at 8 weeks:				
Placebo	7	7	0	14
Zopiclone	8	4	2	14

erate estimate of variance (s^2). Thus at appeared levels of pressure pain threshold s^2 was below 1.0 (range 0.12-0.65) (Table I).

Reported undesired effects of treatment

Reports of suspected side-effects of treatment were somewhat more prevalent in the zopiclone group, with seven reports from patients on zopiclone and three reports from placebo treated patients. Patients on placebo reported gastrointestinal symptoms/nausea, cardiac arrythmia; one patient suspected a venous thrombosis in her leg, which proved not to be true. Patients on zopiclone reported bitter taste of medication (two patients), nightmares and headache (one patient), diarrhoea (two patients), nausea (one patient), and one patient reported simultaneous daytime tiredness, obstipation and numbness in both hands in the morning. None of the experienced side-effects were classified as severe.

Patient self-assessment and examiner assessment of improvement

At eight weeks 4 (29%) of the patients in the placebo group felt that their condition had improved, whereas 6 patients (43%) in the zopiclone group felt an improvement (Table II). In the placebo group most patients considered their condition unchanged, whereas in the zopiclone group an equal number felt improved or worse at 8 weeks. The examiner considered that the condition of 7 (50%) placebo patients and 7 (50%) zopiclone patients had improved at 8 weeks (Table II).

Effect of treatment on tender point sensitivity

In the placebo group most patients had a decreased tender point sensitivity at 4 weeks (9 patients, 64%) and again at 8 weeks (8 patients, 57%), whereas 8 patients (57%) on zopiclone had an increased sensitivity at 8 weeks.

Effect of treatment on global sleep score and morning stiffness score

Surprisingly, more than half of the patients on placebo had improved sleep scores at both 4 weeks and 8 weeks. In the zopiclone group, however, there was even greater improvement (Table III), with 13 (93%) patients having improved sleep scores at 4 weeks and 11 patients (79%) at 8 weeks (vs. 9 patients, 64.3% on placebo at 8 weeks). These differences between groups did not reach statistical significance. At 8 weeks 8 (57.1%) zopiclone patients experienced less morning stiffness vs. 7 patients (50%) in the placebo group. Whereas most of the zopiclone patients felt less morning stiffness at 8 weeks, a similar number of patients in the placebo group reported their condition as improved or unchanged at 8 weeks (Table III).

Effect of treatment on global visual analogue (VAS) sum scores for general discomfort and for pain only

According to the global VAS score 7 patients (50%) in the placebo group felt an improvement at 8 weeks, whereas similar improvement was noted in 8 (57%) zopiclone patients. Similarly, most patients in both groups noted an improvement at 4 weeks. When VAS scores for pain only were compared, eight (57%) placebo patients and 7 (50%) zopiclone patients showed improvement at 8 weeks, again with improvement for most patients in both groups at 4 weeks and 8 weeks (not shown).

Effect of treatment on pain drawing scores

Global pain drawing scores were improved in 8 (57%) placebo patients at 8 weeks, whereas they were worse for 9 (64%) zopiclone patients and improved in only 4 patients (29%). Pain drawing scores for pain only were improved in the placebo group in 6 (43%) patients at 8 weeks, whereas they were worse for half of the patients on zopiclone and only 4 patients showed improvement. An almost equal number of patients on placebo were improved and worse at 8 weeks (not shown).

DISCUSSION

Treatment of fibromyalgia has proven to be quite difficult and no single effective treatment has yet been presented (5, 10-13), even if in a recent study combined treatment with ibuprofen and alprazolam showed a favourable effect on some patients with primary fibromyalgia (14) and the S2- receptor blocker ketanserin appeared promising in a pilot study (15).

Previously reported favourable effects of zopiclone on sleep disturbance (16) were also observed in the present study. At both 4 weeks and 8 weeks most patients reported a better subjective global sleep score, even if improvement in this respect was also seen in more than half of the patients on placebo. The good effect in the placebo group may mask the true effect of the active drug. Other assessment scores were affected by zopiclone treatment to a lesser extent. At 8 weeks, self-assessment by the patient indicated more improvement in the zopiclone group but most patients in the placebo group considered their condition unchanged. An almost equal number of zopiclone patients, however, considered their condition as improved or worse at 8 weeks and according to examiner assessment there was no difference between groups. Tender point sensitivity, VAS and pain drawing scores indicated very little difference between groups. Morning stiffness was also reported similar by both groups at 8 weeks, even if most zopiclone patients considered their condition better, whereas an equal number of patients on placebo considered their condition as improved or unchanged. For most assessments there was a high number of patients on placebo responding favourably, perhaps partly due to inadequacy of assessment methods (17).

The results of the present study confirm those recently reported by Drewes et al. (5), with a marked effect of the drug on measures of subjective sleep complaints, whereas other subjective complaints of fibromyalgia patients, such as pain were not affected to an appreciable extent by zopiclone treatment in either study.

Some methodological aspects should however be further discussed. Even though patients were randomized by an uninvolved party, the number of patients that had to be excluded from the study for various reasons was fairly high, as has also been observed in previous long-term drug studies on fibromyalgia patients. This may reflect frustration when pain and discomfort are inadequately relieved despite ongoing treatment (14). In the present study, escape medication would perhaps partly have reduced the number of patients dropping out during the course of the study. In addition, seven (29 percent) of the twenty-four patients randomized to the zopiclone group experienced what they interpreted to be drug side-effects and wanted to discontinue taking the drug; none of the side-effects however were severe.

With 67 percent of the patients originally found eligible completing the study, patients not included may have affected results. To minimize such bias, the zopiclone and placebo groups completing the study were matched with respect to baseline sleep scores, age distribution, duration of pain and number of patients working. In addition, plotting of baseline scores for each assessment showed no distortion of the scores of excluded patients as compared with the distribution of all patients. Thus, it is likely that patients completing the entire study were fairly well representative of the larger patient sample originally found to be eligible for the study.

In summary, zopiclone appears to have only marginal effects on several different measures of tenderness, pain and discomfort, when the proportion of patients responding is compared to a placebo group. The extent of pain typical of fibromyalgia (3) was also assessed by dolorimeter measurement, VAS scales and pain drawings. The tested drug did not reduce the wide range of the disease. However, the high proportion of patients responding in the placebo group may partly have masked more limited treatment effects. A larger patient mate-

rial would probably also be required to detect such effects.

Acknowledgements: Support by Rhone-Poulenc Rorer, Helsinki, Finland is gratefully acknowledged.

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Received: 10 March 1992,
Revision-accepted: 31 August 1992,
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