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The effect of fluoxetine on sleep: a longitudinal, double-blind polysomnographic study of healthy volunteers

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Fluoxetine, a selective inhibitor of serotonin (5-HT) uptake, was compared with placebo in a randomized double-blind longitudinal trial in 12 healthy volunteers. Sleep polygraphic recordings were performed at home twice before and once after 6 days of medication. After 6 days fluoxetine significantly decreased the amount of rapid eye movement (REM) sleep. The sleep-onset latency and REM latency were increased, but there was no significant increase in the amount of awakenings during night. The relative proportion of stages 2 and 3 increased after fluoxetine administration, although there was no significant change with regard to total amount of slow-wave sleep. Fluoxetine did not induce prominent eye movements during non-rapid eye movement (NREM) sleep in this study. Results of the subjective assessment revealed tendencies of improved sleep and well-being in the fluoxetine group. It is concluded that a comparatively small dose of fluoxetine (20 mg/day) causes the same type of changes in REM sleep which are characteristic of most antidepressive drugs.

Keywords: Double-blind – Fluoxetine – Healthy volunteers – Placebo-controlled – Polysomnography – Sleep

INTRODUCTION

The antidepressive effect of fluoxetine, a selective serotonin (5-HT) uptake inhibitor, has been proved in several controlled studies (Benfield *et al.*, 1986; Young *et al.*, 1987; Debus *et al.*, 1988; Muijen *et al.*, 1988; von Bardeleben *et al.*, 1989a; Corne and Hall, 1989; Kerkhofs *et al.*, 1990). To date, relatively few investigations of the effect of fluoxetine on the sleep of healthy subjects have been published (Nicholson and Pascoe, 1988; Nicholson *et al.*, 1989; von Bardeleben *et al.*, 1989b; Saletu *et al.*, 1991). In these studies, only single doses of fluoxetine were used, and contrary to clinical practice fluoxetine was administered in the evening (except for the study by Saletu *et al.*, 1991). Moreover, the investigators were unable to show any significant effect of fluoxetine on sleep parameters with daily doses less than 60 mg (Nicholson and Pascoe, 1988; Nicholson *et al.*, 1989) or 40 mg (Saletu *et al.*, 1991). In hospital the commonly used daily dose of fluoxetine is 20 mg and it is usually administered in the morning. The half-life of the elimination of fluoxetine is about 96 h (Benfield *et al.*, 1986). According to the data of Saletu and Grünberger (1985) the maximal CNS efficacy occurs between 8 and 10 h after ingestion of fluoxetine. Hence it is unlikely that a single dose of fluoxetine in the evening would reflect the changes in sleep patterns seen in conditions resembling those in which the antidepressant is used in clinical practice. Shenck *et al.* (1992) reported a marked increase in prominent eye movements during non-rapid eye movement (NREM) sleep in 41 fluoxetine-treated patients suffering from either depression or obsessive-compulsive disorder. The sleep recordings of these patients were analysed retrospectively and 48.8% of cases exhibited prolonged runs of high-voltage rapid and slow eye movements which were present during most of stages 1 and 2 sleep. To our knowledge this phenomenon has not been studied in healthy volunteers treated with fluoxetine.

The aim of our study was to investigate the effect of fluoxetine on the sleep of healthy subjects in conditions which with regard to dose and time would be more compatible with the clinical use of fluoxetine.

METHODS

From medical personnel five healthy males and seven females between 23 and 39 (mean 28.7) years were enrolled. None suffered or had previously suffered from any sleep disorders, psychiatric disorders or other major disorders and none was on any regular medication. None had used any hypnotic or other psychoactive medication for at least 3 months prior to the study. No subject was working in the night-shift during or 2 weeks prior to the

study. No medications other than the studied drugs (fluoxetine or placebo) were allowed. The subjects were instructed not to drink alcohol for 2 days before and during the experimental nights. Drinking of coffee was allowed only during the first half of the day on the days preceding the sleep registrations. The study was designed as a randomized double-blind placebo-controlled trial. Each subject ingested fluoxetine 20 mg or an identical capsule of placebo after awakening in the morning for 6 days. Sleep was registered twice on consecutive nights before taking fluoxetine or placebo and once after 6 days of medication.

Submental bilateral electromyographic (EMG), two-channel electrooculographic (EOG; electrodes posited at approximately 1 cm above and slightly lateral to the outer canthus of one eye and approximately 1 cm below and slightly lateral to the outer canthus of the other eye with reference electrodes on the same mastoid bone), and electroencephalographic (EEG) activity from the C4 and A2 positions were registered using silver-silver chloride electrodes and portable four-channel tape-recorders (Oxford Medilog). The electrodes were attached in the sleep laboratory in the evening and the subjects were then transported to their homes where they slept under usual conditions. They were instructed to avoid disturbing factors (to switch off the telephone etc.) during the experimental nights and to switch on the tape recorder when they intended to start sleeping (lights out), and to switch off the tape recorder when they got up in the morning (lights on).

The analogue signals of the recordings were replayed on the Oxford play-back unit (PB-2) and converted to digital signals by the Nightingale Sleep Polyanalyzer. All recordings were then scored visually at 30 s intervals on the screen of the Nightingale Sleep Polyanalyzer according to the Rechtshaffen and Kales criteria (Rechtshaffen and Kales, 1968). Sleep onset was defined as the first epoch of sleep. Sleep latency was defined as the time from lights out until sleep onset and rapid eye movement (REM) latency as the time from sleep onset to the first epoch of REM sleep. The actual sleep time was defined as the time spent in NREM or REM sleep stages. The actual sleep period was defined as the time from sleep onset to lights on. The sleep efficiency index was defined as the time spent in sleep (stages 1, 2, 3, 4, or REM) divided by the time in bed (lights out until lights on).

After awakening the subjects completed a subjective assessment of sleep. Each morning a sleep log was filled out and sleep quality was subjectively evaluated using an ordinal scale from 0 to 10 (0 = very poor sleep, 10 = excellent sleep). The Symptom Check List-90 (SCL-90) inventory was filled out twice, immediately before the start of the medication and on the last day of medication. SCL-90 (Derogatis *et al.*, 1973) is widely known and quite well tested as a self-report questionnaire (Peveler and Fairburn, 1990). It comprises 90 items which reflect nine primary symptom dimensions or subscales: somatization (12 items), obsessive-compulsive (10 items), interpersonal sensitivity (9 items), depression (13 items), anxiety (10 items), anger-hostility (6 items), phobic anxiety (7 items), paranoid ideation (6 items), and psychoticism (10 items). Every one of these 90 items can be estimated according to a 5 point scale from 0 (not at all) to 4 (extremely).

Statistics

Mean values and standard deviations (S.D.) or standard errors of mean (S.E.M.) of the variables were calculated. The Wilcoxon signed ranks test was used for testing non-parametric variables, and the Student dependent *t*-test was used for testing non-parametric variables.

RESULTS

REM sleep

The effect of fluoxetine on REM sleep is shown in Table I. After 6 days of fluoxetine the REM latency increased ($p = 0.046$). The relative ($p = 0.010$) and absolute amount ($p = 0.022$) of stage REM sleep decreased significantly ($p = 0.012$) as did the REM/NREM ratio ($p = 0.021$).

NREM sleep

The results of the effect of fluoxetine on other sleep parameters are given in Tables II and III. Fluoxetine increased the sleep latency ($p = 0.028$), but there was no significant change of the actual sleep time. There was no increase in the number of awakenings, total wake time or wake time after sleep onset, and the decrease of the sleep efficiency index ($p = 0.028$) seemed to be connected only with the increased sleep latency. As illustrated in Table III, fluoxetine increased the relative proportion of stage 2 ($p = 0.028$) and stage 3

TABLE I. REM parameters before and after 6 days of either fluoxetine ($n = 6$) or placebo ($n = 6$)

Measure	Before	S.D.	After	S.D.	*p*
REM latency (min)					
Placebo	67.6	15.0	60.5	14.0	0.417
Fluoxetine	69.0	12.1	106.2	39.4	0.046*b
Total stage REM (min)					
Placebo	121.1	51.8	137.5	54.4	0.345b
Fluoxetine	128.5	16.1	83.0	35.5	0.022*
Total stage REM (% of actual sleep time)					
Placebo	27.7	10.0	29.6	3.6	0.463b
Fluoxetine	28.4	1.8	19.9	5.2	0.010*
REM/NREM ratio					
Placebo	0.40	0.21	0.43	0.08	0.704
Fluoxetine	0.36	0.07	0.25	0.08	0.021*

p values refer to Student's *t*-test (for normally distributed parameters) or Wilcoxon signed ranks test (b) (for not normally distributed parameters). *$p < 0.05$.

TABLE II. Various sleep parameters before and after 6 days of either fluoxetine ($n = 6$) or placebo ($n = 6$)

Measure	Before	S.D.	After	S.D.	p
Sleep onset latency (min)					
Placebo	6.9	3.9	15.9	29.5	0.345b
Fluoxetine	13.6	11.9	24.0	11.2	0.028*b
Sleep onset to stage 2 (min)					
Placebo	9.7	5.4	7.2	7.3	0.593
Fluoxetine	7.3	10.5	3.3	1.4	0.500
Sleep onset to stage 3 (min)					
Placebo	19.3	6.6	24.9	7.5	0.248
Fluoxetine	24.5	7.5	18.8	8.1	0.168
Actual sleep period (min)					
Placebo	440.3	82.3	466.3	121.3	0.465
Fluoxetine	477.0	56.6	419.8	137.0	0.290
Actual sleep time (min)					
Placebo	431.3	80.9	443.9	120.2	0.917b
Fluoxetine	441.7	80.1	387.7	120.1	0.271
Sleep efficiency index					
Placebo	0.96	0.013	0.92	0.065	0.181
Fluoxetine	0.92	0.043	0.84	0.106	0.028*b
Total wake time (min)					
Placebo	16.3	3.4	31.7	27.7	0.206
Fluoxetine	39.5	15.4	48.8	12.4	0.214
Wake time after sleep onset (min)					
Placebo	9.3	3.3	15.8	11.2	0.116b
Fluoxetine	25.9	22.8	24.9	11.8	0.528
Number of awakenings					
Placebo	10.3	5.2	13.3	6.8	0.221
Fluoxetine	16.8	7.4	16.6	6.0	0.940
Number of arousals					
Placebo	5.0	1.3	5.2	4.5	0.922
Fluoxetine	5.7	4.6	7.7	5.3	0.429
Number of awakenings and arousals					
Placebo	15.3	5.8	18.5	10.4	0.363
Fluoxetine	22.5	10.1	24.3	9.7	0.666

p values refer to Student's t-test (for normally distributed parameters) or Wilcoxon signed ranks test (b) (for not normally distributed parameters). *$p < 0.05$.

sleep ($p = 0.024$), but with regard to slow-wave sleep (stages 3 and 4) no changes were observed.

Prominent eye movements during NREM sleep were observed in only one of the subjects treated with fluoxetine. However, this subject exhibited the same pattern of prominent eye movements during NREM sleep at baseline before the fluoxetine medication was initiated.

Self-rating tests

The results of the subjective assessments of sleep quality during the experimental sessions are given in Table IV. This test revealed some tendencies towards improved subjective sleep quality in the fluoxetine group during nights 5-7 ($p = 0.102$). The SCL-90 index of interpersonal sensitivity on the last day of the trial compared with the situation before the medication showed a significant decrease in the fluoxetine group (Wilcoxon signed ranks test: fluoxetine $p = 0.038$; placebo $p = 0.588$). Also the total score of the SCL-90 showed a slight tendency to decrease (Wilcoxon signed ranks test: fluoxetine $p = 0.116$; placebo $p = 0.753$).

TABLE III. NREM parameters before and after 6 days of either fluoxetine ($n = 6$) or placebo ($n = 6$)

Measure	Before	S.D.	After	S.D.	p
Total stage 1					
Placebo	43.6	18.4	46.2	18.4	0.844
Fluoxetine	28.4	14.8	17.1	6.3	0.230b
Total stage 2					
Placebo	165.6	45.3	189.5	49.0	0.310
Fluoxetine	239.3	55.4	241.0	70.8	0.931
Total stage 3 (min)					
Placebo	58.2	21.6	47.6	24.4	0.630
Fluoxetine	34.6	6.7	38.4	9.0	0.482
Total stage 4 (min)					
Placebo	42.4	38.4	25.0	24.0	0.347
Fluoxetine	21.8	25.4	16.9	16.6	0.479
Total slow-wave sleep (min)					
Placebo	100.8	53.0	74.4	48.7	0.437
Fluoxetine	59.3	26.8	55.2	18.0	0.883
Total stage 1 (% of actual sleep time)					
Placebo	10.6	5.8	10.9	10.7	0.753b
Fluoxetine	6.1	2.7	4.4	2.2	0.367
Total stage 2 (% of actual sleep time)					
Placebo	38.5	8.8	42.9	6.6	0.192
Fluoxetine	52.4	6.5	61.9	6.5	0.028*b
Total stage 3 (% of actual sleep time)					
Placebo	13.7	4.7	10.4	4.9	0.311
Fluoxetine	7.8	2.1	10.1	3.7	0.024*
Total stage 4 (% of actual sleep time)					
Placebo	9.2	8.1	5.9	5.6	0.353
Fluoxetine	5.0	6.2	3.4	3.7	0.352
Total slow-wave sleep (% of actual sleep time)					
Placebo	22.9	9.3	16.3	6.2	0.240
Fluoxetine	12.7	7.1	13.5	5.1	0.628

p values refer to Student's t-test (for normally distributed parameters) or Wilcoxon signed ranks test (b) (for not normally distributed parameters). *$p < 0.05$.

DISCUSSION

After 6 days' administration of fluoxetine in a dose of 20 mg clear-cut changes of REM sleep parameters were revealed. Fluoxetine markedly reduced the total amount of REM sleep and also the REM/NREM ratio decreased significantly. Furthermore, there was an increase in the REM latency. Fluoxetine caused an increase in the sleep latency and a decrease in the sleep efficacy index but did not alter the number of awakenings, total wake time or wake time after sleep onset in a statistically significant way. Nor was the actual sleep time or the actual sleep period affected. Fluoxetine is generally believed to be a drug with alerting properties (Stokes, 1993) and thus it might seem surprising that no effect of fluoxetine was seen on total wake time or wake after sleep onset. This may, however, be due to the small number of subjects in this study, as fluoxetine is generally believed to cause insomnia only in a minority of sub-

TABLE IV. Mean scores of the self-rated sleep quality of nights 1-8. Subjective ordinal scale between 1 (very poor sleep) and 10 (excellent sleep)

Night	Mean score fluoxetine	S.E.M.	Compared with night 2 *p*	Mean score placebo	S.E.M.	Compared with night 2 *p*
1	6.2	1.66		7.2	0.80	
2	7.6	0.98		7.4	0.68	
3	7.4	0.98	0.317	7.8	0.37	0.577
4	8.8	0.49	0.180	8.4	0.68	0.059
5	8.4	0.93	0.102	7.8	0.74	0.785
6	8.8	0.58	0.109	7.6	0.60	0.785
7	8.6	0.75	0.102	7.6	0.68	0.713
8	7.4	1.03	0.786	8.0	0.55	0.480

p = *p* values for Wilcoxon signed ranks test. Medication (fluoxetine or placebo) started in the morning after night 2.

jects and may occasionally cause drowsiness and increased sleep in some subjects (Stokes, 1993). No changes in slow-wave sleep were observed and the decrease in REM sleep in the fluoxetine group seemed to be compensated by an increase in stage 2 and 3 sleep. Fluoxetine did not induce prominent eye movements during NREM sleep after 6 days of treatment. Considering the high frequency of this phenomenon (48.8%) reported by Shenck *et al.* (1992), this may indicate that either longer times of fluoxetine treatment and/or concomitant psychiatric or other disorders are required to produce prominent eye movements during NREM sleep. Interestingly, the subjective measurements of sleep quality showed a slight tendency towards improvement in the fluoxetine group in spite of the prolonged sleep latency, shortened sleep period, and the inhibition of the REM sleep. This finding is somewhat surprising when the characteristic pharmacodynamic properties of the substance are taken into consideration.

Our findings concerning the qualitative effects of fluoxetine on sleep architecture are in accordance with those of Nicholson and Pascoe (1988) and Nicholson *et al.* (1989) in healthy volunteers after a single 60 mg dose of fluoxetine. In contrast to our findings, these authors were unable to show any effect of fluoxetine in doses smaller than 60 mg. This could probably be explained by the pharmacokinetic properties of fluoxetine and the single-dose experimental design applied by the authors cited above.

According to several authors (Vogel, 1975) the majority of antidepressant drugs are REM sleep inhibitors. According to our data this is also true for fluoxetine even in the smallest dose (20 mg) commonly used in clinical practice after treatment of approximately 1 week.

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