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Fundamental Research

Sleep Laboratory Studies on the Single-Dose Effects of Serotonin Reuptake Inhibitors Paroxetine and Fluoxetine on Human Sleep and Awakening Qualities

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Summary: Paroxetine is a novel antidepressant drug with selective serotonin (5-HT) reuptake inhibitory properties. In a double-blind placebo-controlled crossover sleep laboratory study the single-dose effects on objective and subjective sleep and awakening qualities were investigated after paroxetine 20, 30 and 40 mg morning doses (PX 20, 30, 40), paroxetine 30 mg evening dose, fluoxetine 40 mg morning dose (FX 40) and placebo in 18 healthy young volunteers. The drugs were orally administered in 2-wk intervals. In addition to each drug night, the adaptation night and washout night were recorded. Polysomnographic investigations (10:30 p.m. to 6:00 a.m.) showed a delayed sleep onset only after the morning intake of paroxetine, PX 40 being statistically different from placebo. Total sleep time and sleep efficiency deteriorated under morning PX 30, PX 40 and evening PX 30 as compared to placebo. The nocturnal wake time and sleep stage 1 increased under the paroxetine. Rapid eye movement (REM) reduction (min and %) occurred dose dependently after all paroxetine doses, but the REM latency was lengthened only after the morning intake. The suppressant effect on REM sleep is characteristic for antidepressants and was still significant in the washout nights following PX 40 and evening PX 30. The only statistically relevant finding under 40 mg fluoxetine referred to the increase of REM latency in both drug and washout nights. In contrast to objective results, subjective sleep quality remained generally unchanged. Attention, concentration and reaction performance improved under paroxetine as compared to baseline. The deterioration of well-being under PX 40 might be related to the appearance of drowsiness and nausea. Blood pressure and pulse rate were unaffected. **Key Words:** Antidepressant—Serotonin (5-HT) reuptake inhibitor—Paroxetine—Fluoxetine—Human sleep—Awakening quality—Polysomnography—Psychometry.

Guided by the biogenic amine theory of depression (1,2) and the assumption that noradrenaline (NA) and serotonin (5-HT) uptake inhibition is an essential mechanism of antidepressants (3), considerable research efforts were invested in developing drugs with selective actions on uptake mechanisms. They were regarded as therapeutic innovation in terms of better efficacy and specificity of effects on the core symptoms of depression on the one hand and with minor side effects on the other hand. Paroxetine is a novel phenylpiperidine compound, which is currently undergoing clinical trials as an antidepressant and which acts centrally as a potent, long-acting and selective 5-HT reuptake inhibitor (4,5). This inhibition of the uptake of 5-HT into the presynaptic terminal is thought to increase the amount of 5-HT in the synaptic cleft and therefore potentiate serotoninergic action. Paroxetine has no appreciable effects on NA uptake, exceptionally weak anticholinergic properties and less effects on the cardiovascular system than classical antidepressants with mixed NA and 5-HT uptake inhibition (6). All metabolites of paroxetine are much less potent than the parent compound and do not contribute to the activity of paroxetine (7).

Pharmacokinetic studies in man (8,9) showed peak plasma levels between 2 and 6 hr after single oral doses, an elimination half-life of around 16 hr and approximated first pass effects (hepatic extraction) of around 50%. Only 1–2% of the parent compound was excreted in the urine, indicating that paroxetine is almost completely metabolized. During multiple doses (10–40 mg/day), paroxetine steady state was reached within a week.

Clinical trials on paroxetine have been conducted

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TABLE 1. *Sleep initiation and maintenance on baseline, under paroxetine 20-, 30-, 40-mg morning doses, fluoxetine 40-mg morning doses, paroxetine 30-mg evening doses and placebo (n = 18)*[a]

	Baseline (A)	PX 20 (B)	PX 30 (C)	PX 40 (D)
Latency to stage 1 (min)	18.1 (17.9)	31.3 (42.5)	28.8 (37.3)	28.1 (27.1)
Latency to stage 2 (min)	21.2 (19.2)	35.9 (43.3)	32.8 (37.5)	32.7 (27.4)*
Latency to stage 3 (min)	43.5 (47.4)	47.8 (44.9)	47.9 (37.6)	47.9 (32.0)
Latency to stage 4 (min)	58.6 (56.2)	100.9 (133.0)	100.6 (132.4)	97.1 (129.6)
REM latency (min)	90.7 (43.0)	183.9 (98.2)**	234.2 (140.8)**	259.7 (133.1)**
Total sleep period (min)	427.2 (18.3)	409.8 (59.1)	415.9 (36.3)	417.9 (28.4)
Total sleep time (min)	398.0 (41.3)	381.4 (66.3)	380.4 (39.9)	371.8 (33.4)*
Sleep efficiency (%)	89.4 (9.2)	85.5 (14.7)	85.4 (9.1)	83.3 (7.5)*
Wake/TSP (min)	24.9 (36.7)	23.7 (35.2)	31.3 (31.0)	41.1 (35.3)
Wake/before buzzer (min)	0.0 (0.0)	4.8 (18.3)	1.0 (3.4)	0.1 (0.4)
No. of awakenings/TSP	4.9 (4.6)	5.3 (5.2)	7.9 (8.0)	7.6 (6.7)

[a] All values are mean (SD).
* $p < 0.05$; ** $p < 0.01$, as compared to baseline (Wilcoxon test).
† $p < 0.05$; †† $p < 0.01$, interdrug differences (multiple Wilcoxon).

with more than 2,000 patients worldwide. So far, analyses of results from completed studies (10–14) have shown paroxetine to exert an overall antidepressant effect with an optimal therapeutic range of 20–50 mg/day. Higher doses caused a slight increase of adverse events, especially nausea, but these were minimized if the initial dose was titrated. There have been no unexpected tolerance problems.

Paroxetine, like zimelidine, prolonged waking and shortened slow-wave sleep and paradoxical sleep in animals (15). In a double-blind sleep laboratory study in volunteers (16), paroxetine given either on the preceding morning or at bedtime caused more frequent awakenings, reduced total sleep and strongly suppressed rapid eye movement (REM) sleep and, in the former administration regime, additionally delayed sleep onset and increased slow-wave sleep.

The aim of the present double-blind placebo-controlled study was to examine the single-dose effects of paroxetine (given either the previous morning or evening) on objective and subjective sleep and awakening qualities as compared to another 5-HT uptake inhibitor, fluoxetine, in healthy young volunteers.

METHODS

Subjects

Eighteen physically and mentally healthy volunteers (nine females, nine males), ranging in age from 24 to 36 yr (mean 28.7 yr), weighing between 51 and 90 kg (mean 63.7 kg) and ranging in height from 162 to 192 cm (mean 173.4 cm) were included in this double-blind placebo-controlled crossover study. Subjects did not take any psychoactive medication in the 2 wk prior to and/or during the trial. They were allowed moderate ingestion of alcohol and caffeine-containing beverages during the study but abstained from such consumption 24 hr before the start until the end of each treatment period. The study was performed in accordance with the requirements of the Declaration of Helsinki (Tokyo amendment). A written informed consent was obtained.

Study design

Subjects spent 20 nights in the sleep laboratory. One initial adaptation night (in order to familiarize with the recording procedures) and one baseline night were followed by six treatment periods. Each treatment period included one adaptation night, one drug night and one washout night. The drugs were orally administered in 2-wk intervals in a balanced Latin Square design in the morning (7:30 a.m., before breakfast) and evening (10:00 p.m., half an hour before polysomnographic investigations). Six dosages were administered; they are abbreviated in the present article as follows:

PX 20 = 20 mg paroxetine morning dose + placebo evening dose;
PX 30 = 30 mg paroxetine morning dose + placebo evening dose;
PX 40 = 40 mg paroxetine morning dose + placebo evening dose;
FX 40 = 40 mg fluoxetine morning dose + placebo evening dose;
Evening PX 30 = placebo morning dose + 30 mg paroxetine evening dose;
Placebo = placebo given in the morning and evening.

Polysomnographic investigations

Polygraphic all-night recordings were performed between 10:30 p.m. (lights out) and 6:00 a.m. (buzzer) in two identically shielded rooms; thus the total time in bed was fixed. The electrodes were attached ac-

TABLE 1. *Continued*

FX 40 (E)	Evening PX 30 (F)	Placebo (G)	Interdrug differences
19.7 (22.5)	15.8 (18.8)	22.3 (41.1)	D:F†
25.6 (26.8)	18.7 (19.6)	24.8 (41.5)	D:F, G†
37.6 (28.5)	31.4 (21.1)	40.2 (44.1)	
67.9 (99.2)	85.1 (133.2)	144.7 (172.9)	
131.0 (69.0)*	98.5 (64.8)	104.6 (46.7)	B:A††, F†; C:A, F††; D:A, F, G††
421.7 (27.9)	427.4 (20.2)	423.0 (42.5)	
397.8 (35.4)	369.7 (67.7)	409.0 (45.3)	C:G†; D:G††; F:G††
89.4 (7.8)	83.0 (15.3)	91.6 (10.0)	C:G†; D:G††; F:G†
18.6 (28.3)	52.5 (65.3)	9.1 (15.1)	D:G†; F:G†
3.4 (14.6)	2.0 (5.8)	0.9 (4.0)	
4.2 (3.4)	7.4 (6.9)	4.3 (5.2)	

cording to the international 10/20 system. In addition to the electroencephalographic (EEG) channels C4-A1, O2-A1 and Cz-02, two electrooculographic (EOG) channels and the submental electromyogram (EMG) were recorded on 8-channel R611 Beckman polygraphs. Four channels (Cz-02, EMG and two EOG) were also recorded on a Hewlett-Packard 3968 tape recorder. Thirty-second epochs were scored according to the criteria of Rechtschaffen and Kales (17). Sleep prints and variables were obtained by means of a Hewlett-Packard Vectra computer system.

Total sleep time (TST) is the amount of actual sleep time in the total sleep period (TSP). TSP is the period of time measured from sleep onset until final awakening. In addition to TST, TSP included wake time (wake/TSP) and movement time. The number of awakenings refers to the arousals to wakefulness during TSP. The sleep efficiency index is the proportion of sleep in the recorded period, and it is calculated by dividing TST by the total time in bed (TIB) multiplied by 100. Sleep stages 1, 2, 3, 4 and REM are expressed in minutes and in percentages of the TST. Latency to stage 1, 2, 3 and 4 defines the period of time measured from lights out to the appearance of sleep stage 1, 2, 3 and 4, respectively. REM latency is defined as clock time from first epoch of stage 2 (followed by ≥8 min sleep in the next 10 min) to the first REM period of at least 3 min (18). Wake/before buzzer is the time spent awake from the final awakening until the buzzer. Stage shifts refer to the number of shifts from one stage to another during the TIB.

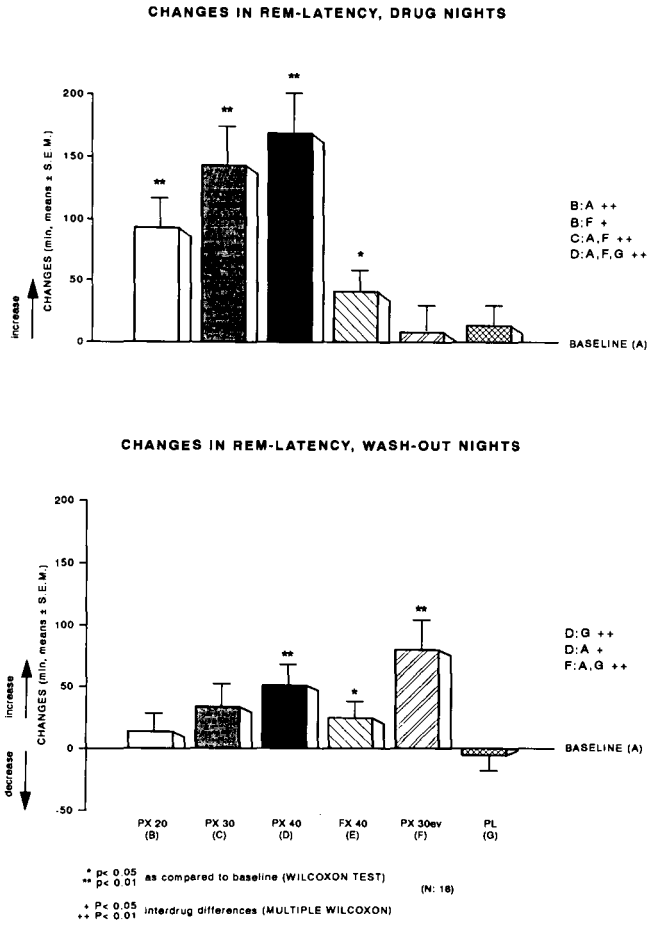

FIG. 1. Changes in REM latency (drug nights, washout nights) after paroxetine morning (PX 20, 30, 40 mg) and evening doses (PX 30 ev), fluoxetine (FX 40 mg) and placebo (PL) (n = 18). REM latency was dose-dependently lengthened after the morning intake of paroxetine as compared to baseline, while it remained unchanged after evening PX 30 mg. Fluoxetine (morning dose) caused only a small increase. REM latency was significantly lengthened in washout nights after PX 40 mg and more so after evening PX 30 mg. Fluoxetine increased REM latency too, although to a slight degree.

Awakening quality and subjective sleep quality

At 6:00 a.m. subjects were awakened by acoustic stimuli (1,000-Hz tone, 1 sec long), which started at 35 dB and increased stepwise (10 dB) at 1-min intervals to 94 dB until the subject awakened. The loudness of

TABLE 2. *Sleep architecture on baseline, under paroxetine 20-, 30-, 40-mg morning doses, fluoxetine 40-mg morning doses, paroxetine 30-mg evening doses and placebo (n = 18)*[a]

	Baseline (A)	PX 20 (B)	PX 30 (C)	PX 40 (D)
Stage 1 (min)	13.0 (6.9)	17.9 (17.0)	22.3 (17.1)	26.5 (21.4)*
Stage 1 (%)	3.4 (2.0)	5.1 (5.0)	6.0 (4.7)	7.1 (5.9)**
Stage 2 (min)	228.0 (44.2)	224.3 (44.4)	227.8 (41.0)	228.0 (39.3)
Stage 2 (%)	57.4 (10.3)	59.0 (6.7)	59.8 (7.5)	61.6 (10.9)
Stage 3 (min)	41.3 (18.3)	44.6 (18.2)	42.1 (18.0)	38.6 (20.6)
Stage 3 (%)	10.3 (4.3)	11.6 (4.1)	11.1 (4.6)	10.5 (6.0)
Stage 4 (min)	37.6 (25.3)	43.1 (27.3)	44.7 (25.3)	43.5 (28.7)
Stage 4 (%)	9.2 (5.9)	11.5 (7.2)	11.8 (6.5)*	11.5 (7.4)
Stage 3 + 4 (min)	78.9 (35.5)	87.7 (28.8)	86.8 (27.8)	82.1 (34.9)
Stage 3 + 4 (%)	19.5 (7.9)	23.2 (7.3)	22.9 (7.2)	22.0 (9.1)
Stage REM (min)	78.1 (24.4)	51.5 (26.7)**	43.5 (28.6)**	35.2 (28.2)**
Stage REM (%)	19.7 (6.1)	12.8 (6.2)**	11.3 (7.2)**	9.3 (7.4)**
No. of REM periods	3.4 (1.0)	2.4 (1.2)*	2.0 (1.2)**	1.7 (1.4)**
Stage shifts/time in bed	55.4 (14.0)	57.3 (16.8)	61.8 (23.3)	64.4 (20.7)
Movement time (min)	4.2 (2.1)	4.8 (4.0)	4.1 (2.2)	5.0 (2.8)

[a] All values are mean (SD).
* $p < 0.05$; ** $p < 0.01$, as compared to baseline (Wilcoxon test).
† $p < 0.05$; †† $p < 0.01$, interdrug differences (multiple Wilcoxon).

the tone that awakened the subject determined the awakening threshold.

After the morning toilet the volunteers completed a self-rating scale on their subjective quality of sleep and awakening (Selbstbeurteilungsbogen für Schlaf- und Aufwachqualität = SSA) (19). Subsequently, they participated in a series of psychometric tests: The Grünberger alphabetical cross-out test (Alphabetischer Durchstreichtest = AD) for quantification of attention (AD/total score), concentration (AD/E%; errors in percentage of the total score) and attention variability (AD/SV; difference between extreme scores) (20), the numerical memory test (20), as well as the Grünberger fine motor activity test (right and left hand) for evaluation of changes in psychomotor activity and drive (20). Reaction time, reaction time variability (msec) and the errors of omission and commission were determined by the computer-assisted reaction time apparatus. The von Zerssen B-S scale (21) was completed for evaluation of well-being in the evening and in the morning. Drive, mood, affectivity and drowsiness were measured by means of 100-mm visual analogue scales. Psychophysiological investigations included the critical flicker frequency (CFF, descending threshold) after awakening; muscle strength of the right and left hand, as well as of the right and left index finger and thumb was evaluated by means of the vigorimeter (kp/cm^2) (22). The evening and morning pulse rate and blood pressure were also recorded.

Statistical analyses

Exploratory statistical analyses included the Friedman's test, the multiple Wilcoxon, and the Wilcoxon tests.

As there were no statistically significant differences between baseline and placebo with the sole exception of drowsiness (which was more pronounced under placebo than baseline), the following significant changes under paroxetine and fluoxetine are described with respect to placebo only. However, detailed statistical analyses including comparison versus baseline are presented in the tables. For washout nights those variables showing statistically significant changes are explained in the results section.

RESULTS IN DRUG NIGHTS

Findings under paroxetine

Sleep initiation and maintenance

There was a similar magnitude of increase in latency to stage 1 after PX 20, 30 and 40 (morning drug administration). In contrast, the evening PX 30 showed a decreased latency to stage 1 that was statistically different from PX 40 (Table 1). The mean change of latency to stage 2 increased after PX 20, 30 and 40. It became significant with PX 40 as compared to placebo and evening PX 30. The latencies to stages 3 and 4 showed no significant interdrug differences. The morning intake of paroxetine lengthened REM latency in a dose-related manner, whereas evening PX 30 did not (Fig. 1). The difference between morning and evening paroxetine was statistically significant. Sleep efficiency and total sleep time deteriorated significantly under PX 30 and PX 40 as well as under evening PX 30 as compared to placebo. Total sleep period and the wake time before buzzer did not show statistically relevant drug-induced changes. Wake time within TSP was significantly longer after PX 30 and PX 40 than after

TABLE 2. *Continued*

FX 40 (E)	Evening PX 30 (F)	Placebo (G)	Interdrug differences
13.6 (6.3)	24.4 (15.7)**	12.2 (11.2)	D:G††, A†; F:G††
3.5 (1.7)	7.6 (6.8)**	3.1 (3.1)	D:G††, A, E†; F:G††
234.4 (37.7)	227.8 (59.7)	239.7 (36.4)	
58.9 (7.7)	61.1 (9.3)*	58.7 (6.3)	
38.8 (15.6)	38.8 (18.0)	45.3 (20.2)	
9.8 (3.9)	10.4 (4.3)	11.0 (4.4)	
42.2 (26.0)	38.4 (25.7)	34.6 (27.4)	
10.6 (6.6)	10.5 (6.5)	8.4 (6.4)	
81.0 (30.0)	77.2 (30.0)	79.9 (27.1)	
20.4 (7.8)	20.9 (7.4)	19.3 (5.5)	
68.8 (15.3)	40.3 (26.2)**	77.2 (15.1)	C:A, G††; D:A, E, G††; F:A:, G††
17.3 (3.5)	10.5 (6.1)**	18.9 (3.4)	B:A†; C:A††, G†; D:A, E, G††; F:A, G†
2.9 (0.8)	2.6 (1.4)*	3.6 (0.9)	C:G††, A†; D:A, G††
56.4 (14.8)	66.7 (22.6)*	56.2 (20.0)	
5.4 (2.7)*	5.2 (3.1)	4.8 (2.4)	

placebo, whereas the number of nocturnal arousals remained unchanged.

Sleep architecture

Sleep stage 1 (in minutes and percentage of TST) was lengthened under paroxetine in a dose-related manner (Table 2). PX 40 and evening PX 30 could be distinguished from placebo and PX 40 also from FX 40, the latter being practically equal to placebo. Stage 2 (in percentage) increased slightly after evening PX 30 and stage 4 (in percentage) increased slightly after morning PX 30. Sleep stage REM (in minutes and percentage) was shortened after morning and evening paroxetine. This effect was dose related, so that only PX 20 could not be differentiated from placebo, whereas the most pronounced REM reduction occurred after PX 40, which was also statistically different from FX 40. With regard to the number of REM periods, only PX 30 and PX 40 caused a significant decrease as compared to placebo, whereas evening PX 30 did not. The number of stage shifts increased slightly after evening PX 30.

Subjective sleep and awakening quality

Self-assessment of the quality of sleep (SSA-1) and awakening (SSA-2) did not reveal any significant findings (Table 3). Somatic complaints in the morning (SSA-3) increased slightly under evening PX 30 and the SSA total score demonstrated a worsening after PX 40. The latter dosage deteriorated the evening and morning well-being as compared to placebo. The 100-mm analogue scales demonstrated an impairment of drive, mood, affectivity and drowsiness after PX 40 and less so after evening PX 30.

TABLE 3. *Subjective sleep and awakening quality on baseline, under paroxetine 20-, 30-, 40-mg morning doses, fluoxetine 40-mg morning doses, paroxetine 30-mg evening doses and placebo (n = 18)*[a]

		Baseline (A)	PX 20 (B)	PX 30 (C)	PX 40 (D)	FX 40 (E)	Evening PX 30 (F)	Placebo (G)	Interdrug differences
Sleep quality (SSA-1)	↓[b]	11.6 (4.3)	11.6 (3.7)	11.7 (4.4)	13.7 (4.3)	12.2 (4.7)	12.9 (4.2)	9.8 (2.8)	
Awakening quality (SSA-2)	↓	14.8 (4.3)	13.2 (2.8)	14.0 (3.4)	16.6 (4.4)	14.9 (4.3)	17.6 (5.2)	13.9 (3.6)	
Somatic complaints (SSA-3)	↓	6.0 (1.3)	6.4 (1.6)	5.9 (1.1)	6.4 (1.6)	5.5 (1.2)	6.9 (1.5)*	5.7 (0.9)	
Total score (SSA)	↓	32.4 (8.0)	30.9 (6.8)	31.7 (6.9)	36.7 (8.3)*	32.6 (7.9)	37.3 (6.8)	29.4 (5.3)	
Well-being evening	↓	9.7 (7.2)	9.2 (6.9)	8.1 (6.4)	17.3 (12.8)*	10.2 (10.1)	11.1 (11.0)	7.6 (9.2)	D:G††
Well-being morning	↓	9.7 (7.9)	8.1 (6.2)	11.7 (11.9)	17.9 (13.8)**	10.0 (11.2)	15.6 (12.9)	10.6 (11.7)	D:G†
Drive	↓	34.1 (23.7)	36.1 (25.6)	44.7 (28.7)	52.9 (26.2)**	33.7 (23.6)	51.3 (21.9)*	40.2 (30.6)	D:A†
Mood	↑	77.4 (15.2)	74.8 (20.5)	68.9 (24.7)	60.7 (20.2)**	72.9 (20.6)	66.8 (19.5)*	69.9 (22.3)	
Affectivity	↑	73.7 (19.3)	77.8 (15.9)	66.4 (28.1)	59.8 (25.5)*	71.6 (19.5)	60.3 (22.7)*	65.8 (27.9)	
Drowsiness	↓	35.1 (21.3)	43.5 (28.1)	43.8 (25.9)	59.1 (24.2)**	45.2 (29.0)	61.6 (24.0)*	53.7 (27.9)*	D:A†

[a] All values are mean (SD).
[b] ↑↓Direction of improvement.
* $p < 0.05$; ** $p < 0.01$, as compared to baseline (Wilcoxon test).
† $p < 0.05$; †† $p < 0.01$, interdrug differences (multiple Wilcoxon).

TABLE 4. *Objective awakening quality on baseline, under paroxetine 20-, 30-, 40-mg morning doses, fluoxetine 40-mg morning doses, paroxetine 30-mg evening doses and placebo (n = 18)*[a]

	Baseline (A)	PX 20 (B)	PX 30 (C)
Awakening threshold (dB)	58.2 (20.3)	58.8 (24.1)	52.8 (19.3)
Attention (AD/total score)	407.9 (107.0)	422.3 (98.2)	445.3 (124.6)*
Concentration (AD/E%)	4.4 (3.8)**	3.2 (3.0)	3.7 (3.3)
Attention variability (AD/SV)	13.7 (4.6)	12.8 (3.8)	13.9 (6.2)
Numerical memory	6.8 (1.6)	7.1 (2.0)	7.1 (2.0)
Fine motor activity (right)	48.8 (6.4)	51.3 (7.0)	47.4 (6.3)
Fine motor activity (left)	39.1 (8.3)	38.2 (6.9)	38.2 (10.8)
Fine motor activity (total)	88.1 (11.0)	89.4 (11.2)	85.6 (14.8)
Reaction time (msec)	457.3 (121.2)	428.1 (139.8)	420.4 (132.4)
Reaction time variability (msec)	88.7 (37.1)	89.8 (48.7)	79.8 (33.4)
Reaction, errors (omission)	0.4 (0.8)	0.4 (1.2)	0.2 (0.7)
Reaction, errors (commission)	1.3 (1.0)	1.2 (1.1)	0.7 (1.3)

[a] All values are mean (SD).
* $p < 0.05$; ** $p < 0.01$, as compared to baseline (Wilcoxon test).
† $p < 0.05$; †† $p < 0.01$, interdrug differences (multiple Wilcoxon).

Objective awakening quality

The awakening threshold did not reveal significant drug-induced changes (Table 4). Attention (AD/total score) improved under PX 30 and concentration (AD/E%) improved under PX 20 and evening PX 30 as compared to baseline. Attention variability was unaffected. Reaction time and reaction time variability appeared to be better under active treatment, the former variable especially under evening PX 30 and the latter under PX 40. The Grünberger fine motor activity test and numerical memory did not reveal significant results.

The morning critical flicker frequency remained unchanged after paroxetine as compared to placebo, but interdrug comparison showed a significant difference between morning and evening PX 30 with a higher frequency after the latter (Table 5). Muscle strength of the left finger, as measured by the vigorimeter, slightly improved after PX 40. With respect to hemodynamic parameters the only relevant finding was an elevated pulse rate in the evening after the morning intake of PX 30.

Findings under fluoxetine

Sleep initiation and maintenance

The small increase of REM latency was the only statistically relevant finding under FX 40 (Fig. 1).

Sleep architecture

There were no changes in sleep architecture under FX 40 with the sole exception of slightly augmented movement time (Table 2).

TABLE 5. *Psychophysiological measurements on baseline, under paroxetine 20-, 30-, 40-mg morning doses, fluoxetine 40-mg morning doses, paroxetine 30-mg evening doses and placebo (n = 18)*[a]

	Baseline (A)	PX 20 (B)	PX 30 (C)	PX 40 (D)	FX 40 (E)	Evening PX 30 (F)	Placebo (G)	Interdrug differences
CFF (Hz)	41.5 (4.2)	41.1 (3.8)	40.8 (2.9)	41.6 (2.9)	41.9 (3.5)	41.8 (4.2)	40.7 (3.1)	C:F†
Vigorimeter right finger	0.4 (0.1)	0.5 (0.1)	0.4 (0.1)	0.4 (0.1)	0.5 (0.1)	0.4 (0.1)	0.5 (0.1)	
Vigorimeter left finger	0.4 (0.1)	0.5 (0.1)	0.4 (0.1)	0.5 (0.1)*	0.5 (0.1)	0.4 (0.1)	0.4 (0.1)	
Vigorimeter right hand	0.7 (0.2)	0.7 (0.2)	0.6 (0.2)	0.7 (0.2)	0.7 (0.2)	0.6 (0.2)	0.7 (0.2)	
Vigorimeter left hand	0.7 (0.2)	0.7 (0.2)	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)	0.6 (0.2)	0.7 (0.2)	
Evening systolic BP (mmHg)	112.2 (12.5)	115.6 (10.1)	111.7 (8.7)	111.2 (10.6)	110.8 (9.6)	108.9 (10.1)	109.4 (10.3)	
Evening diastolic BP	74.2 (7.1)	76.4 (8.5)	73.3 (5.4)	76.4 (5.4)	76.4 (9.5)	76.1 (7.0)	75.1 (6.6)	
Evening pulse (beats/min)	70.1 (11.2)	69.7 (12.5)	74.2 (11.5)*	70.9 (10.9)	71.6 (11.3)	74.6 (10.3)	73.1 (13.1)	
Morning systolic BP	110.6 (8.9)	109.4 (11.1)	109.4 (11.1)	110.4 (6.4)	113.3 (8.0)	111.4 (7.8)	109.2 (11.8)	
Morning diastolic BP	74.7 (8.3)	75.3 (9.3)	75.8 (8.3)	73.6 (5.1)	76.7 (6.6)	76.7 (6.2)	74.4 (8.2)	
Morning pulse	69.1 (10.1)	71.8 (11.3)	68.9 (11.7)	67.3 (10.7)	67.9 (11.7)	68.8 (7.5)	68.8 (6.8)	

[a] All values are mean (SD); BP, blood pressure.
* $p < 0.05$; ** $p < 0.01$, as compared to baseline (Wilcoxon test).
† $p < 0.05$; †† $p < 0.01$, interdrug differences (multiple Wilcoxon).

TABLE 4. *Continued*

PX 40 (D)	FX 40 (E)	Evening PX 30 (F)	Placebo (G)	Interdrug differences
50.6 (17.4)	49.0 (19.0)	52.2 (19.4)	59.3 (20.6)	
420.9 (116.8)	449.4 (112.5)*	435.7 (120.4)	420.2 (107.8)	
3.6 (4.0)	3.8 (5.1)	2.8 ((2.4)*	3.8 (3.9)	
12.6 (5.6)	12.2 (5.4)	14.1 (5.4)	12.4 (5.1)	
6.9 (1.7)	7.3 (2.3)	6.8 (2.0)	6.8 (1.6)	
48.0 (9.2)	49.4 (9.2)	49.3 (6.6)	47.9 (7.6)	
37.0 (10.8)	39.3 (11.4)	38.9 (10.7)	38.3 (10.5)	
85.0 (14.6)	88.7 (16.1)	88.3 (13.9)	86.3 (13.8)	
417.8 (127.3)	405.1 (153.9)	407.7 (110.0)*	426.8 (130.6)	
77.8 (32.2)*	74.9 (36.9)	78.4 (37.7)	87.7 (39.4)	
0.1 (0.5)	0.1 (0.2)	0.2 (0.5)	0.1 (0.3)	
0.9 (0.8)	1.4 (1.1)	0.9 (1.3)	0.9 (1.2)	

Subjective sleep and awakening quality

Subjective sleep and awakening quality remained unchanged under FX 40.

Objective awakening quality

Attention improved under fluoxetine as compared to baseline.

RESULTS IN WASHOUT NIGHTS

Findings under paroxetine

Objective sleep quality

Sleep latencies remained unchanged. With regard to sleep maintenance the only statistically relevant finding in washout nights was a small decrease of the wake time within TSP under PX 30 and placebo as compared to baseline ($p < 0.05$, Wilcoxon test). Sleep stage 2 (in percentage) was slightly augmented after withdrawal from PX 40 as compared to baseline ($p < 0.05$, Wilcoxon test). Deep sleep revealed no drug-induced changes. The REM sleep (in minutes and percentage) was still significantly attenuated in the washout nights after PX 40 and evening PX 30 as compared to the washout nights after placebo ($p < 0.05$, multiple Wilcoxon). The number of REM periods decreased under evening PX 30 as compared to placebo ($p < 0.01$, multiple Wilcoxon). PX 40 and evening PX 30 lengthened REM latency (Fig. 1) as compared to placebo ($p < 0.01$, multiple Wilcoxon).

Awakening quality

Concerning self-rating scales and psychometric tests there were no relevant interdrug differences.

Findings under fluoxetine

Objective sleep quality

Sleep stage 2 (in percentage) was slightly augmented after withdrawal from FX 40 as compared to baseline ($p < 0.05$, Wilcoxon test). REM latency was lengthened in washout nights after FX 40 as compared to baseline ($p < 0.05$, Wilcoxon test) (Fig. 1).

Awakening quality

Concerning self-rating scales and psychometric tests there were no relevant interdrug differences.

DISCUSSION

In this single-dose sleep laboratory investigation in healthy volunteers involving different times of application of serotonin reuptake inhibitors, the morning administration of paroxetine lengthened sleep latency, with the PX 40 being statistically different from placebo, whereas paroxetine taken at bedtime did not influence sleep initiation. Presumably, absorption of the late dosage was too slow to be effective. Sleep maintenance, determined by means of nocturnal wake time, total sleep time and sleep efficiency, deteriorated dose dependently not only when the drug was given in the morning, but also after the evening PX 30. Sleep-disturbing effects disappeared during washout. The present results agree with those of Oswald and Adam (16) in reportedly poor sleepers (mean age 57 yr) who received paroxetine likewise either in the morning or at bedtime (15 mg, 30 mg); early and middle insomnia increased.

Quantitative EEG analysis and evaluation of plasma concentrations of paroxetine in healthy volunteers (23) showed activating effects (significant decrease of delta

and theta power below 8 Hz and increase in beta activity above 12 Hz) at or around peak plasma concentrations, 6 hr after single doses of 70 mg. These findings were consistent with the pharmaco-EEG profiles of other serotonin reuptake inhibitors, such as sertraline (in the lower and well-tolerated dosage range) (24), zimelidine (24,25), fluvoxamine (26,27) and fluoxetine (28). All of them have been characterized as antidepressants with alerting qualities. Deteriorated sleep initiation and sleep efficiency could be expected in polysomnography as activating properties should come to the fore. However, changes noted on paroxetine, even though statistically significant, are small (within 1 SD of baseline and placebo values) and are unlikely to be of clinical importance. This is supported by self-rating scales where subjective sleep quality remained unchanged.

Sleep-disturbing effects obtained after single doses may not persist with multiple exposure. Recently published EEG sleep measures (29) showed an immediate but only transient increase of sleep onset and sleep continuity difficulties in fluvoxamine-treated (3 wk) inpatients with major depression. Restoration to the approximate predrug levels occurred by the third week of administration. Only REM-suppressive effects for fluvoxamine were sustained.

The major paroxetine-induced changes concerned sleep architecture, where REM sleep was markedly suppressed as compared to placebo, while stage 1 increased. No consistent delta sleep alterations were found. The REM reduction was dose related; it occurred with PX 20, followed by morning as well as evening PX 30 and was most pronounced under PX 40. The amount of time spent in REM sleep was still significantly shortened in washout nights after PX 40 and evening PX 30. REM latency increased dose dependently under morning paroxetine and was still significantly lengthened during PX 40 washout. After evening PX 30, REM latency increased only in washout nights. The time of the pharmacodynamic peak might have been reached late in the observation period and therefore the effect could not be seen during the drug night but appeared more readily after withdrawal.

In the last decade sleep research in depression has focused on REM latency, as shortening was frequently observed in both endogenous and neurotic depressions (30–34). It is of interest that antidepressant drugs have a suppressent effect on REM sleep in patients and healthy volunteers as well (35–39). This was also true for the selective 5-HT reuptake inhibitors fluvoxamine (29,40) and fluoxetine (41). Paroxetine falls in line.

Under 40-mg fluoxetine morning doses, the only statistically relevant finding was the increase of REM latency in drug nights and washout nights as compared to baseline. The rather subtle changes might be due to the pharmacokinetic properties of fluoxetine, characterized by the rather late peak plasma concentrations around the sixth hour and the long half-life of approximately 70 hr (42). Previous pharmaco-EEG analysis showed only mild encephalotropic effects when recordings were carried out as usual up to 10 hr after single oral doses of fluoxetine (30, 60, 75 mg) (28); maximal pharmacodynamic changes (increased alpha activity, decreased slow activity and decreased fast beta activity) occurred between the 8th and 10th hour postdrug.

Morning attention, concentration, reaction time and reaction time variability tended to improve after paroxetine in a nondose-related manner as compared to baseline. Fluoxetine had a beneficial effect on attention too. The improvement in psychometric performance was in accordance with previous pharmacodynamic studies in serotoninergic antidepressants (24,26,28). Blood pressure, pulse rate and psychophysiological variables were unaffected.

All volunteers completed the study, but they complained occasionally of drowsiness and nausea, especially under PX 40, which could be the reason for the significant deterioration of well-being. Early morning behavior returned to baseline during washout. Nausea, diarrhea and restlessness are common side effects of selective serotonin reuptake inhibitors (43,44), whereas anticholinergic effects are minor. Because in our study the medication was given only once, and because it has been reported that paroxetine is well tolerated during prolonged administration (10–14), we hypothesize that during prolonged treatment eventually some tolerance to sleep-disturbing and gastrointestinal side effects may develop. In light of this possibility and the findings of the present study we intend to address this question in a followup study with an extended period of medication (4 wk) in order to reach steady-state concentrations of the compound.

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