The Effects of Fluoxetine on the Polysomnogram of Depressed Outpatients: A Pilot Study

William A. Hendrickse, M.D., Howard P. Roffwarg, M.D., Bruce D. Grannemann, M.A., Paul J. Orsulak, Ph.D., Roseanne Armitage, Ph.D., John W. Cain, M.D., John Battaglia, M.D., John R. Debus, M.D., and A. John Rush, M.D.

The effects of fluoxetine (FLU) and its active metabolite, norfluoxetine (NFLU), on the polysomnogram (PSG) of nine depressed outpatients (eight with major depression; one with bipolar II, depressed phase disorder) were investigated by contrasting PSG values prior to treatment and during administration of FLU. The PSG changes were correlated with daily dose, cumulative dosage, single serum concentrations, and the total area under the serum concentration curve (AUC) of both FLU and NFLU.

Fluoxetine clearly increased both stage 1 sleep time and rapid-eye-movement (REM) latency and decreased both percent REM and REM density. With a few exceptions, the cumulative dosage of FLU and the AUC of FLU and NFLU were better predictors of the changes in awake and movement time in the PSG than single-sample concentrations of FLU and NFLU taken at the time of PSG assessment. ***[Neuropsychopharmacology 10:85-91, 1994]***

KEY WORDS: *Fluoxetine; Norfluoxetine; Polysomnography; Serotonin; Depression*

Fluoxetine (FLU)—a potent, specific, serotonin reuptake inhibitor—is an effective treatment for major depression (for a review, see Depression Guideline Panel, 1993). Serotonin affects the regulation of the sleep–wake cycle. It plays a role in the induction and maintenance of sleep as well as the character of sleep-stage macroarchitecture and rapid-eye-movement (REM) sleep expression (Jouvet et al. 1989).

Fluoxetine reportedly causes a shift toward lighter sleep that is reflected in increases in sleep latency and percentage of non-REM stage 1 sleep and decreases in total sleep time, sleep efficiency, and percentage of non-REM stages 3 and 4 sleep (Nicholson and Pascoe 1986; Pastel and Fernstrom 1987; Kerkhofs et al. 1990; Keck et al. 1991; Keck and McElroy 1992). The duration of REM sleep and REM latency, as well as REM density, may also be affected by FLU (Nicholson and Pascoe 1988; von Bardeleben et al. 1989; Nicholson et al. 1989; Bakalian and Fernstrom 1990; Hanzel et al. 1991; Saletu et al. 1991). These effects likely depend upon both the dose and duration of FLU treatment.

Changes in polysomnogram (PSG) measures associated with chronic FLU treatment in depressed subjects have been incompletely studied (Schenck et al. 1992). Relationships among PSG measures and serum concentrations of FLU and its active metabolite norfluoxetine (NFLU) have not been previously reported in depressed patients. This pilot study evaluated the effect of FLU and NFLU on PSG measures in a group of medication-responsive depressed outpatients.

From the Mental Health Clinical Research Center and Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas.

Address reprint requests to: William A. Hendrickse, M.D., MHCRC at St. Paul Professional Bldg. I, Suite 600, 5959 Harry Hines Blvd., Dallas, Texas 75235-9101.

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METHODS

Subjects

Subjects were selected from a pool of self-referred patients (n = 5) and symptomatically depressed volunteers (n = 4) who were recruited by local advertisements. Following a screening visit, potential subjects had full clinical evaluations, which included administration of the Structured Clinical Interview for DSM-III-R (Spitzer et al. 1986). Evidence of general medical, sleep, or neurologic disorders was exclusionary. Only nonsteroidal, antiinflammatory agents were permitted during the 2-week period preceding PSG evaluations. Depressive symptom severity was measured by the 17-item Hamilton Rating Scale for Depression (HDRS-D) (Hamilton 1960) and the 30-item Inventory of Depressive Symptomatology, Clinician-Related Version (IDS-C) (Rush et al. 1986).

At the time of the study, diagnosis for all patients was nonseasonal, nonpsychotic, major depression, single or recurrent type, with moderate to severe symptoms, as evidenced by a 17-item HDRS-D score greater than 16. Patients with a history of any other psychiatric disorder, including psychoactive substance abuse, were dropped from consideration for the study. No subject had ever received prior treatment with FLU. Table 1 describes the sample.

Table 1. Sample Characteristics

	Full Sample (n = 9)
Demographics	
Age	37.3 ± 10.6
Female	44.4%
Major depression[a]	100.0%
Number of episodes	2.7 ± 1.5
Current episode length (months)	19.3 ± 21.4
Age at onset (yrs)	28.6 ± 11.6
Pretreatment symptom severity	
HDRS-D score	21.9 ± 4.7
IDS-C score	38.9 ± 9.2
Posttreatment symptom severity	
HDRS-D score	7.8 ± 2.5
IDS-C score	14.3 ± 9.1
Prior course of illness	
Single episode	22.2%
Recurrent	67.7%
Measures of fluoxetine exposure	
T_2 dose (mg/day)	36.7 ± 10.0
T_2 cumulative dose (total mg)	2884.4 ± 1345.5
T_2 FLU concentration (ng/ml)	342.3 ± 152.5
AUC FLU concentration	21951.7 ± 11200.1
T_2 NFLU concentration (ng/ml)	404.4 ± 160.6
AUC NFLU concentration	25634.3 ± 13288.8
T_2 FLU + NFLU (ng/ml)	746.8 ± 301.5
AUC FLU + NFLU concentration	47586.1 ± 23939.6

[a] Includes eight patients with major depression and one with bipolar II, depressed phase disorder.

Patients received FLU in an open-label fashion and were managed under standard clinical guidelines. Weekly evaluations included completion of the 17-item HDRS-D and the 30-item IDS-C. Fluoxetine was initiated at a dose of 20 mg/day (AM administration). The dose was increased initially to 40 mg/day if remission did not occur within 6 weeks. Treatment compliance was monitored by patient self-report.

Procedures

Each subject's requirement for and adequacy of nocturnal sleep had been identified and firmly established in advance of both PSG assessments. During the week preceding these recordings, patients maintained a 5-day sleep diary to document regularity of bed and rise times, nightly net sleep, and sleep quality. Napping was proscribed. Each patient retired and rose at individualized clock times. These were established following consultation with the patient and examination of the information recorded in the patient's sleep diary.

Prior to treatment with FLU, baseline PSG assessments were conducted during 2 consecutive nights in the Department of Psychiatry Sleep Study Unit of the University of Texas Southwestern Medical Center. All patients were drug free for at least 2 weeks prior to the initial night of PSG recording.

The electroencephalogram (EEG) was recorded from central sites referenced to contralateral ear lobes (C3–A2, C4–A1) on a polygraph (GRASS model 78; Quincy, MA) equipped with 7P-511 AC amplifiers set at a sensitivity of 5. The half-amp low- and high-frequency bandpass filters were set at 0.3 and 30 Hz, respectively (24 dB/octave). A 60-Hz notch filter attenuated electrical noise. Electrodes and transducers were also affixed during the first night of baseline sleep assessment to identify respiratory disturbances and periodic limb movement disorder.

A second series of 2-night PSG evaluations was conducted "on drug" after 7 to 29 weeks (median 11.9 weeks) of treatment (T_2). At T_2, the individualized doses ranged from 10 to 50 mg/day (36.7 ± 10.0), prescribed in once-a-day or alternating daily regimens. At T_2, seven of nine patients had achieved remission, which occurred between the 3rd and 14th week (median 8.0 weeks) of treatment with FLU. Remission was defined as an HDRS-D score less than or equal to 9 and an IDS-C score less than or equal to 14 for at least 2 consecutive weeks. The remaining two subjects responded significantly (T_2 HDRS-D score = 11.0 ± 1.4). Table 2 shows the PSG parameters at baseline (T_1) and after the acute treatment phase (T_2).

Visual sleep-stage scoring was performed according to standardized criteria (Rechtschaffen and Kales 1968) by personnel trained to better than 90% agreement. Polysomnogram parameters that were computed

Table 2. Polysomnographic Variables at T_1 and T_2 for Nine Subjects

Variables Analyzed as T_1–T_2 Differences	Pretreatment (Drug Free) (T_1)	Posttreatment (On Drug) (T_2)
TIB (min)	477.0 ± 24.3	481.3 ± 32.2
TSP (min)	423.1 ± 43.2	406.7 ± 40.7
TST (min)	379.9 ± 53.9	355.6 ± 62.0
REM Latency (min)[a]	86.3 ± 26.7	147.4 ± 69.5*
% Stage REM in TSP	14.7 ± 5.3	11.4 ± 4.2*
REM Density	2.1 ± 0.5	2.6 ± 0.7*
AMT in TSP (min)	43.8 ± 31.1	51.6 ± 32.5
AMT in first 1/3 TIB (min)	70.8 ± 29.2	74.8 ± 40.3
AMT in second 1/3 TIB (min)	35.9 ± 33.5	51.8 ± 43.6
AMT in third 1/3 TIB (min)	60.9 ± 50.8	51.6 ± 44.1
Stage 1 min in TSP	73.6 ± 21.1	125.6 ± 40.4*
Stage 2 min in TSP	228.9 ± 29.2	179.8 ± 59.7
Stages 3 and 4 min in TSP	13.6 ± 16.9	3.1 ± 4.9
% Sleep efficiency[b]	79.6 ± 10.0	74.3 ± 14.1
% Sleep efficiency minus stage 1[c]	73.1 ± 7.5	62.9 ± 20.0
Sleep latency (min)	35.8 ± 12.3	42.0 ± 23.0

[a] Includes AMT.
[b] (TST ÷ TIB).
[c] (TST − Stage 1 ÷ TIB).
* $p < .05$ based on paired t-test uncorrected for number of comparisons.

at T_1 and T_2 included 1) total time in bed (TIB)—time in minutes from "lights out" to "lights on"; 2) onset of total sleep period (TSP)[1]—the time of appearance of the half-minute epoch that initiates the first 10-minute period of recording that includes at least 8 minutes of any stage of non-REM sleep or the first epoch of REM sleep, whichever is sooner; 3) sleep latency—time from "lights-out" to onset of TSP; 4) wake-up time (WUT)—the first epoch of wake following the last 10-minute period of sleep that contains at least 8 minutes of any stage of sleep; 5) total sleep time (TST)—net minutes of sleep within TSP; 6) awake and movement time (AMT)—total minutes of AMT in the TSP and also in the first, second, and third one-thirds of the night; 7) stage 3 plus stage 4 sleep—total minutes of stage 3 combined with stage 4; 8) sleep efficiency—percentage of TST in total TIB; 9) sleep efficiency minus non-REM stage 1 sleep—percentage of TST minus non-REM stage 1 in total TIB; and 10) REM latency—time from onset of TSP to the first half-minute epoch of REM sleep. REM density was scored on a 0 to 4-point scale for each minute of REM sleep. Polysomnogram variables were averaged across nights for each subject at each measurement occasion (T_1 and T_2). Additional details relevant to scoring criteria are presented by Emslie et al. (1990).

Weekly serum samples were obtained in the morning approximately 24 hours after the last medication dose, before ingestion of medication for that day. Blood was drawn for analysis at 8 AM (range 8 to 10 AM) following the second night of PSG recording at T_2.

[1] Total sleep period is often referred to as the period of persistent sleep.

Fluoxetine and NFLU were isolated from serum by liquid–liquid extraction. They were then separated and quantified by reverse-phase, high-performance liquid chromatography (HPLC) with ultraviolet detection. Units reported are ng/ml. Within-run precision was determined, yielding a coefficient of variation between 0.0% and 5.1% for FLU and 1.3% and 7.7% for NFLU. The between-run coefficient of variation was 4.1% to 6.8% for FLU and 6.2% to 8.8% for NFLU (Orsulak et al. 1988).

Statistical Analyses

The statistical analyses were divided into three parts. First, to test for changes in PSG between T_1 and T_2, we conducted paired t-tests. Second, to measure the relationship between the FLU exposure and changes in PSG, correlations between these measures were conducted. Third, we estimated sample sizes needed to replicate the finding based on the regression results with power set at .80 and alpha at .05. All statistical analyses were computed using a commercially available software program (SAS Institute Inc. 1988).

Contemporaneous FLU measures used in the analyses included 1) current FLU dose; 2) FLU serum concentration; 3) NFLU serum concentration, and 4) total (FLU plus NFLU) serum concentration. Additional parameters designed as measures of cumulative effects of FLU treatment were cumulative oral dose at T_2 and total area under the serum concentration curve (AUC) for FLU and NFLU (i.e., the serum concentration analogs of cumulative oral dose). Cumulative FLU dose and AUC encompass the entire treatment period. The AUC was estimated by a straight-line fit. A polygon was con-

Table 3. Posttreatment (T_2) Correlation of Independent Measures, Dose, and Blood Levels[a]

	Cumulative Dose	FLU AUC	NFLU AUC	Total AUC	T_2 Dose	T_2 FLU Concentration	T_2 NFLU Concentration	T_2 Total Concentration
T_2 dose	0.62	0.65	0.57	0.62	1.00	0.82	0.82	0.85
T_2 FLU concentration	0.37	0.54	0.43	0.49	0.82	1.00	0.85	0.96
T_2 NFLU concentration	0.54	0.68	0.58	0.64	0.82	0.85	1.00	0.96
T_2 total concentration	0.47	0.64	0.53	0.59	0.85	0.96	0.96	1.00
Cumulative dose	1.00	0.94	0.95	0.97	0.62	0.37	0.54	0.47
FLU AUC	0.94	1.00	0.91	0.97	0.65	0.54	0.68	0.64
NFLU AUC	0.95	0.91	1.00	0.98	0.57	0.43	0.58	0.53
Total AUC	0.97	0.97	0.98	1.00	0.62	0.49	0.64	0.59

[a] Pearson product-moment correlation coefficient (n = 9).

structed using the weekly serum concentrations as its height and the days of treatment as its width. The area of the polygons estimated the AUCs for both FLU and NFLU. Inasmuch as contemporaneous and cumulative measures were mathematically related, correlations among them are shown in Table 3.

Table 3 suggests that the four measures of contemporaneous FLU exposure and the four measures of cumulative exposure have considerable overlap within each group of measures. The correlations between the contemporaneous and cumulative measures are lower, suggesting that the current and cumulative measures are less interdependent.

As a caution to the reader, the analyses reported in this paper are exploratory and designed to serve as a guide for future research. Both the t-test of PSG T_1 to T_2 difference scores and the correlations between the exposure to FLU measures and PSG T_1 to T_2 difference scores are considered potentially confounded by the alleviation of depression. Although multivariate statistical analyses can be designed to test and separate the influences of multiple effects, in this study with only a few subjects, it is either impossible to perform such analyses or the results may be misleading because they were conducted on a very small sample. In addition, no attempt was made to statistically correct for the number of tests being used and the probability reported should only be used as a guide to measures that would be useful in future research.

RESULTS

Overall Changes in the Polysomnogram

Results of the t-test of the differences between T_1 and T_2 measures revealed an increase in stage 1 sleep, REM latency and REM density between T_1 and T_2 (Table 2).

Polysomnogram Changes in Relation to Medication Dose and Serum Concentrations

The correlations presented in Table 4 between FLU measures suggest the following relationships: 1) Ease of falling asleep (sleep latency) was affected most by the cumulative dosage and cumulative serum concentration (AUC) of FLU rather than by its contemporaneous dose or concentration at T_2; 2) Intervening wakefulness (AMT) (overall and in the first one-third of the night) were most strongly correlated with contemporaneous FLU dose at T_2; the cumulative exposure measures correlated with AMT in the first one-third of the night, and the cumulative measures of NFLU AUC and total AUC correlated with AMT in the last one-third of the night; 3) sleep efficiency was affected by both the cumulative dosage and serum AUC for FLU as well as current dose.

Findings in the seven treatment remitters were equivalent to those of the group as a whole (n = 9), except for a correlation between FLU AUC and AMT in the third one-third of the night (r = .784) in the remitters, which was not found for the complete sample.

Because these data were collected as a pilot study, we estimated the sample sizes needed to detect a relationship between FLU dose and serum concentrations and changes in PSG measures between T_1 to T_2. Based on these data, a wide range of sample sizes would be needed. For example, samples with 5 to 37 subjects would be sufficient to find significant changes in total AMT in the first and third one-thirds of the night in relation to FLU AUC. In contrast, to find a significant relationship between FLU AUC and minutes of stage 1 sleep would require a sample in the thousands.

DISCUSSION

In this sample of nine depressed patients who underwent sleep studies before and during the course of treatment with FLU, the drug appeared to alter both sleep continuity and sleep-stage architecture. Sleep changes observed between drug-free (pretreatment) and on-medication (posttreatment) conditions were increases in REM latency, stage 1 sleep and REM density, and decreases in percent REM sleep. It appears that sleep shifted from deeper (non-REM stages 2, 3, and 4) to

Table 4. Correlations Between PSG Changes, Dose, and Blood Levels[a]

Variables Analyzed as T_1–T_2 Differences	Cumulative Dose	FLU AUC	NFLU AUC	Total AUC	T_2 Dose	T_2 FLU Concentration	T_2 NFLU Concentration	T_2 Total Concentration
REM latency (min)	−0.14	−0.09	−0.01	−0.05	−0.01	0.31	0.05	0.18
% Stage REM in TSP	0.08	0.06	0.12	0.09	0.56	0.43	0.40	0.43
REM density	−0.31	−0.22	−0.31	−0.27	0.18	0.32	0.37	0.36
AMT in TSP (min)	−0.41	−0.43	−0.35	−0.39	**−0.72**	−0.38	−0.47	−0.44
AMT in first 1/3 TIB (min)	**−0.80**[b]	**−0.86**	**−0.68**	**−0.78**	**−0.81**	−0.57	−0.63	−0.62
AMT in second 1/3 TIB (min)	−0.50	−0.47	−0.32	−0.40	−0.55	−0.16	−0.22	−0.20
AMT in third 1/3 TIB (min)	−0.66	−0.55	**−0.76**	**−0.68**	−0.37	−0.07	−0.30	−0.19
Stage 1 min in TSP	0.17	−0.05	−0.03	−0.04	−0.24	−0.51	−0.62	−0.59
Stage 2 min in TSP	0.63	−0.65	0.54	0.61	**0.68**	0.34	0.57	0.45
Stages 3 and 4 min in TSP	−0.15	−0.33	−0.04	−0.17	−0.09	−0.33	−0.23	−0.29
% Sleep efficiency minus stage 1	−0.08	0.20	0.10	0.15	0.24	0.56	0.64	0.62
% Sleep efficiency	**0.74**	**0.72**	0.62	**0.68**	**0.68**	0.27	0.44	0.37
Sleep latency (min)	**−0.75**	**−0.86**	−0.59	**−0.73**	−0.60	−0.46	−0.56	−0.53

[a] Pearson product-moment correlation coefficients (n = 9).
[b] Correlation coefficients in boldface are less than p = .05.

lighter stages with more wakefulness, although changes in the deeper sleep measures did not reach statistical significance in this small sample.

Cumulative treatment exposure particularly affected ease of falling asleep, conventional sleep efficiency, and wakefulness in the first and last one-thirds of the night. The relationship of NFLU to wakefulness during sleep appeared to be greatest in the latter part of the night. The NFLU AUC correlated strongly with the decline in AMT in the last one-third of the night (reduction in "terminal" insomnia) and may be a marker of the antidepressant effects of FLU. The meager amount of deep non-REM sleep and the great interindividual variability evident at T_1 may explain the poor correlation between the decrements in deep non-REM sleep and FLU treatment (see Table 4). Overall, the cumulative measures appear to be somewhat more sensitive to sleep changes than contemporaneous measures.

The PSG changes that related to FLU and NFLU were in a direction opposite to changes that have been reported when there is a reduction in depressive symptoms. Increased REM latency and REM density and decreased percent REM, which were unrelated to FLU and NFLU measures, have been found with a reduction in depressive symptoms.

Other investigators have found that treatment with FLU affects the sleep of depressed patients (Kerkhofs et al. 1990; Keck et al. 1991). However, Keck et al. (1991) reported baseline PSG data for only one patient in their sample (n = 7). Sleep continuity was disturbed, as exemplified by increases in the number of arousals and sleep-stage shifts. Consistent with our data, the proportion of stage 1 sleep seemed to increase, whereas deep non-REM sleep and sleep efficiency declined.

Suppression of REM sleep has been noted in patients treated with either FLU or amitriptyline (Kerkhofs et al. 1990). Our findings are similar to those of Kerkhofs et al. (1990), but provide an analysis of serum concentrations of FLU and NFLU as well.

Although we also found a lengthening of REM latency, an increase in REM density, and a reduction in overall REM percent, they did not correlate with the amount or duration of FLU treatment in this sample of patients. Such findings suggest that increased REM latency and decreased REM sleep, although occurring following exposure to many types of antidepressant drugs, are not uniquely related to specific characteristics of drug dose and serum concentrations. However, because of the high interindividual variability of the T_2 REM latency in our subjects, a larger sample is needed to support this contention.

Single doses of FLU (20 to 80 mg) also affect the sleep of nondepressed, healthy adults (Nicholson and Pascoe 1988; Nicholson et al. 1989; von Bardeleben et al. 1989; Saletu et al. 1991). Sleep was found to be of poorer quality following a dose of FLU, with a rise in the number of arousals and in stage 1 sleep. Percentage of REM sleep was reduced and REM latency was lengthened, a finding common to many antidepressant medications. However, results from single-dose studies have only a restricted application in the management of major depressive episodes during which antidepressant agents are usually prescribed for weeks or months.

The pharmacodynamic properties of FLU and NFLU probably influence their effects on sleep. Following an oral dose of FLU, peak serum concentrations are reached within 6 to 8 hours. Fluoxetine is extensively metabolized to equipotent NFLU. The long elimination half-life of FLU (2 to 3 days) and NFLU (5 to 9 days) assures a large accumulation of both substances. After multiple doses of FLU, serum concentrations and ratios of FLU to NFLU are unpredictable (Lemberger et

al. 1985; Stark et al. 1985; Benfield et al. 1986; Orsulak et al. 1988; Keck and McElroy 1992). Accumulation of FLU and NFLU in the brain may contribute to both therapeutic and toxic effects (Renshaw et al. 1992).

Chronic alterations in sleep can cause excessive daytime sleepiness. Patients who report this condition may metabolize FLU differently, resulting in an accumulation of NFLU, which in turn, may exacerbate excessive daytime sleepiness. Keck and McElroy (1992) reported plasma FLU/NFLU ratios less than 1.0 in eight patients who reported excessive daytime sleepiness and ratios greater than 1.0 in those who did not report this phenomenon. However, it is also possible that the symptom of excessive daytime sleepiness follows upon the light and disrupted sleep secondary to FLU treatment. Normal subjects have reported drowsiness on the day following a single dose of FLU. They also evidence reduced coding ability and prolonged reaction times (Saletu and Grunberger 1985; Nicholson and Pascoe 1988).

The cumulative effects of FLU may be important in elderly patients who are generally subject to more disturbed sleep and reduced daytime wakefulness than are younger adults (Czeisler et al. 1992; Bliwise 1993). The elderly are sensitive to cumulative effects of drugs, particularly when multiple drugs are administered for concomitant systemic illnesses.

This preliminary study suggests that some of the cumulative effects of FLU and NFLU on sleep (i.e., sleep efficiency, sleep latency) may be different. In addition, the size of sleep changes may depend upon the duration and strength of exposure to one or the other substance. Certain PSG parameters, such as changes in REM latency or deep non-REM sleep, do not appear to correlate specifically with either FLU or NFLU parameters. This interpretation is consistent with the REM sleep differences reported after single doses and after chronic exposures of 30 days or longer, as noted above. A more definitive study is needed to fully evaluate the relative effects on the PSG of cumulative versus contemporaneous measures of FLU treatment.

Finally, several investigators have noted an increase in non-REM eye movements with FLU (Keck et al. 1990; Schenck et al. 1992). Keck et al. (1990) have also shown that FLU-induced eye movements occur most often in stage 1 sleep. These eye movements can potentially compromise sleep-stage discrimination, perhaps resulting in the misclassification of sleep stages. It is possible that the FLU-induced eye movements resulted in an increase in scorable stage 1 sleep, accompanied by a decrease in the identification of stage 2 sleep. This potential sleep-stage misclassification could have resulted in the decrease in stage 2 sleep observed upon treatment in this study. Upon reviewing the PSG records, FLU-induced eye movements create the largest uncertainty in differentiating stage 1 from wakefulness and from REM sleep, which suggests that the decreased stage 2 sleep observed in this pilot study is unlikely to have resulted from sleep-stage misclassification. However, to further clarify this issue, a systematic, quantitative study of the distribution of FLU-induced eye movements across sleep is currently underway, including an assessment of interrater disagreement on sleep-stage classification.

The influence of FLU on sleep does not appear to hinder its efficacy in the acute treatment phase of major depression. Lower doses (e.g., 10 mg/day) than those usually used in the acute treatment phase may produce or sustain a remission of symptoms without the excessive daytime sleepiness found with high serum concentrations of NFLU. Our findings, if replicated, would be consistent with the strategy of lowering the dose of medication in subjects who have responded clinically to FLU, but who subsequently develop an impairment in falling asleep or in maintaining sleep (Cain 1992).

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REFERENCES

Bakalian MJ, Fernstrom, JD (1989): Effects of L-tryptophan and other amino acids on electroencephalographic sleep in the rat. Brain Res 528:300–307

Benfield P, Heel RC, Lewis SP (1986): Fluoxetine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. Drugs 32:481–508

Bliwise DL (1993): Sleep in normal aging and dementia. Sleep 16:40–81

Cain JW (1992): Poor response to fluoxetine: Underlying depression, serotonergic overstimulation or a "therapeutic window"? J Clin Psychiatry 53:272–277

Cohen J (ed) (1988): Statistical Power Analysis for the Behavioral Sciences, 1st ed. Hillsdale, NJ: Lawrence Erlbaum Associates

Czeisler CA, Dumont M, Duffy JF, Steinberg JD, Richardson GS, Brown EN, Sanchez R, Rios CD, Ronda JM (1992): Association of sleep-wake habits in older people with

changes in output of circadian pacemaker. Lancet 340:933–936

Depression Guideline Panel (1993): Clinical Practice Guideline. Depression in Primary Care: Volume 2: Treatment of Major Depression. Rockville, MD: U.S. Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, AHCPR Publication No. 93–0551

Emslie GJ, Rush AJ, Weinberg WA, Rintelmann JW, Roffwarg HP (1990): Children with major depression show reduced rapid eye movement latencies. Arch Gen Psychiatry 47:119–124

Hamilton M (1960): A rating scale for depression. J Neurol Neurosurg Psychiatry 12:56–62

Hanzel DA, Proia NG, Hudgel DW (1991): Response of obstructive sleep apnea to fluoxetine and protriptyline. Chest 100:416–421

Jouvet M, DeNoyer M, Kitahama K, Sallonanon M (1989): Slow wave sleep and indolamines. A hypothalamic target. In Wanquier A, Dugovic C (eds), Slow Wave Sleep, Physiologic and Functional Aspects. New York, Raven Press, pp 91–108

Keck PE Jr, McElroy SL (1992): Ratio of plasma fluoxetine to norfluoxetine concentrations and associated sedation. J Clin Psychiatry 53:127–129

Keck PE Jr, Hudson JI, Dorsey CM, Campbell PI (1991): Effect of fluoxetine on sleep. Biol Psychiatry 29:618–619 (letter)

Kerkhofs M, Rielaert C, de Maertelaer V, Linkowski P, Czarka M, Mendlewicz J (1990): Fluoxetine in major depression: Efficacy, safety and effects on sleep polygraphic variables. Inatl Clin Psychopharmacol 5:253–260

Lemberger L, Bergstrom RF, Wolen RL, Farid NA, Enas GG, Aronoff GR (1985): Fluoxetine: Clinical pharmacology and physiological disposition. J Clin Psychiatry 46:14–19

Nicholson AN, Pascoe PA (1988): Studies on the modulation of the sleep-wakefulness continuum in man by fluoxetine, a 5-HT uptake inhibitor. Neuropharmacology 27:597–602

Nicholson AN, Pascoe PA, Turner C (1989). Modulation of sleep by trimipramine in man. Eur J Clin Pharmacol 37:145–150

Orsulak PJ, Kenney JT, Debus JR, Crowley G, Wittman PD (1988): Determination of the antidepressant fluoxetine and its metabolite in serum by reverse-phase HPLC, with ultraviolet detection. Clin Chem 34:1875–1878

Pastel RH, Fernstrom JD (1987): Short-term effects of fluoxetine and trifluoromethylphenylpiperazine on electroencephalographic sleep in rat. Brain Res 436:92–102

Rechtschaffen A, Kales A (eds) (1968): A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. National Institute of Health Publication 204, Washington, DC, US Government Printing Office.

Renshaw PF, Guimares AR, Fava M, Rosenbaum JS, Pearlman JD, Flood JG, Puopolo PR, Clancy K, Gonzalez G (1992): Accumulation of fluoxetine and norfluoxetine in human brain during therapeutic administration. Am J Psychiatry 149:1592–1594

Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger JE, Burns CT (1986): The Inventory for Depressive Symptomatology (IDS). Psychiatry Res 18:65–87

Saletu B, Grunberger J (1985): Classification and determination of cerebral bioavailability of fluoxetine: Pharmacokinetics, pharmaco-EEG and psychometric analyses. J Clin Psychiatry 46:45–52

Saletu B, Frey R, Krupka M, Anderer P, Grunberger J, See WR (1991): Sleep laboratory studies on the single-dose effects of serotonin reuptake inhibitors paroxetine and fluoxetine on human sleep and awakening qualities. Sleep 14:439–447

SAS Institute Inc (1988): SAS/STAT User's Guide, Release 6.03 ed. Cary, NC, SAS Institute Inc.

Schenck CS, Mahowald MW, Kim SW, O'Connor KA, Hurwitz TD (1992): Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive-compulsive disorder. Sleep 15:226–235

Spitzer RL, Williams JBW, Gibbons M (1986): The Structured Clinical Interview for DSM-III-R (SCID). New York, New York Psychiatric Institute

Stark P, Fuller RW, Wong DT (1985): The pharmacological profile of fluoxetine. J Clin Psychiatry 46:3–6

von Bardeleben U, Steiger A, Gerken A, Holsboer F (1989): Effects of fluoxetine upon pharmacoendocrine and sleep-EEG parameters in normal controls. Int Clin Psychopharmacol 4 (Suppl 1): 1–5