The Effects of Fluoxetine on Quantitative Sleep EEG in Depressed Outpatients

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In previous studies, fluoxetine has been shown to increase light, nonrestorative sleep and to decrease sleep efficiency. This work also suggested that women are more sensitive to the alerting effects of selective serotonin reuptake inhibitors on sleep characteristics. The purpose of the present study was to evaluate the effects of fluoxetine on quantitative sleep EEG. The effects of five and ten weeks of fluoxetine treatment on quantitative sleep EEG were evaluated in 36 patients with major depressive disorders compared to baseline when patients were symptomatic but unmedicated. All patients were treatment responders, achieving symptom remission at week 10. Fluoxetine significantly increased fast-frequency activity and decreased delta during sleep at both 5 weeks and 10 weeks of treatment. Contrary to our expectation, treatment effects on EEG were not stronger in depressed women than men. The protocol also included sleep studies at week 30 of treatment and 7-8 weeks after medication discontinuation. Since only 13/36 (36.1%) patients completed the entire protocol, the effects of fluoxetine on quantitative sleep EEG were compared in study completers versus dropouts. Dropouts showed the largest fluoxetine-induced EEG changes (from baseline to week 10) with greater beta amplitude and lower delta amplitude than study completers. This effect approached significance. It was concluded that fluoxetine is alerting to both standard sleep measure and to quantitative sleep EEG and that these effects may be related to clinical outcome.
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Key words: fluoxetine, depression, sleep EEG

INTRODUCTION

Major depressive disorders (MDD) are associated with a variety of sleep macroarchitectural disturbances, based on visual stage scoring of the sleep electroencephalogram (EEG). These include insomnia, impaired sleep continuity, abnormalities in the amount and timing of rapid eye movement (REM) sleep, reductions in deep non-REM (NREM) sleep, increased awakenings during the night and increased light, nonrestorative Stage 1 sleep (1-3).

Clinically depressed patients also show a number of sleep microarchitectural abnormalities, based on quantitative EEG measurement. Reductions in the amplitude, incidence and distribution of delta activity across NREM sleep have been the most consistent findings (3-11), although not all studies support this finding (12-13).

Sleep microarchitectural abnormalities are also found in faster frequency EEG bands including alpha (11), beta (3, 4-15) and in total EEG power (11). Those with MDD show greater amplitude and incidence of fast-frequency EEG activity during sleep than healthy controls. Of particular interest is the finding that women with MDD appear to have the highest incidence of fast-frequency EEG activity during sleep, yet show more delta activity than depressed men (16-17). Moreover, depressed patients particularly women also show a reduction in temporal coherence of ultradian EEG rhythms (14,17-18).

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While the specific neurobiological mechanisms underlying sleep abnormalities in depression have not been fully explicated, abnormal functions of aminergic and cholinergic neurotransmission appears likely (19-23). Serotonin certainly plays a key role in many of the behaviors associated with depression including mood, sleep, appetite, sexual activity, neuroendocrine functions, temperature, motor activity and cognitive function (2,24-25). Serotonin also affects the induction and maintenance of sleep and the regulation of the sleep/wake cycle (26). Moreover, the amount of REM sleep is regulated by both serotonergic and noradrenergic neurons in the dorsal pontine tegmentum (26-27). Thus, it is reasonable to expect that antidepressant medications with selective serotonergic effects should influence both sleep macro- and microarchitecture in depressed patients.

Selective serotonergic reuptake inhibitors (SSRIs) have been shown to produce mild to moderate REM sleep inhibition in depressed patients — prolonging the latency to REM sleep and reducing total REM time. These effects were evident for fluoxetine (28-32), sertraline (33) and paroxetine (34-35). Both fluoxetine and paroxetine were also alerting to sleep, increasing the number of awakenings and light stage 1 sleep, effects which appear to have clinical relevance. Although both clinicians and patients rate sleep quality as improved on fluoxetine, more than 20% of patients report an increase in the number and duration of awakenings on treatment. This effect is significantly more pronounced in women than in men (36). Thus, sex differences may be evident in the sleep effects of SSRIs.

Although there are a number of preclinical studies that suggest that SSRIs also impact on quantitative sleep EEG (37) few studies have evaluated these effects in depressed patients (38). Nevertheless, it is reasonable to expect that SSRIs would decrease slow-frequency EEG activity and enhance fast-frequency components, based on their alerting effects on sleep macroarchitecture. Moreover, decreased slow-frequency activity may be more prevalent in women with depression, who appear to be more sensitive to the alerting effects of SSRIs (36).

The purpose of the present study was to evaluate the effects of fluoxetine and potential sex differences on quantitative sleep EEG over ten weeks of acute phase treatment in 36 patients with MDD who responded to treatment. Of particular interest was a comparison of fluoxetine-induced EEG changes in study completers versus those who dropped out before the end of the 37-week protocol. Complete sleep macroarchitectural data and clinical assessment are reported elsewhere (32).

METHODS

Subjects

Subjects were selected from a pool of self-referred patients and symptomatically depressed volunteers recruited by local advertisements. Following an initial screening visit and written informed consent, potential subjects underwent full clinical evaluations including the Structured Clinical Interview for DSM-III-R (SCID) (39) administered by a trained clinical evaluator and confirmed by a psychiatrist (M.T.). Depressive symptom severity was measured by the 17-item Hamilton Rating Scale for Depression (HRS-D) (40-41) and the 30-item Inventory for Depressive Symptomatology, both clinician-rated (IDS-C) and self-report (IDS-SR) versions (42-43).

All patients were required to meet DSM-III-R (44) criteria for nonseasonal, nonpsychotic MDD (single or recurrent), with moderate to severe symptomatology (as evidenced by a 17-item HRS-D score‡16) and be between 18 and 50 years of age.

Patients with a history of any other major psychiatric disorder (including psychoactive substance abuse within the previous 12 months) were excluded, as were patients who failed prior adequate treatment with fluoxetine (at least 4 weeks at 20 mg/day). Individuals engaged in shift work within the last 6 months and those with independent sleep disorders (narcolepsy, apnea, bruxism, restless legs or nocturnal myoclonus) established either by history or by polysomnogram (PSG) evaluation were also excluded. Except for nonsteroidal anti-inflammatory agents, all participants were drug-free for at least 2 weeks prior to the baseline sleep study.

Treatment Protocol

Patients received open-label fluoxetine 20 mg/day (a.m. dosing), for at least five consecutive weeks with an increase in dose to 40 mg/day if clinically indicated. Patients who had achieved symptomatic remission at week 10 (HRS-D†10) were continued on the same dose of fluoxetine through week 30 (i.e., an additional 20 weeks), after which fluoxetine was discontinued. Patients were than followed for an additional 6-8 weeks drug-free (week 37).

The complete study protocol (32) called for sleep evaluations at baseline (patients were symptomatic but unmedicated), at weeks 1, 5, 10 and 30 on fluoxetine treatment, and after 8 weeks following medication discontinuation. This present report compared sleep microarchitecture at baseline, weeks 5 and 10 of acute phase treatment in 24 women and 12 men who responded (i.e. those with an HRS-D score of †10 at week 10. Clinical and demographic data on these patients are shown in Table 1.

Table 1. Demographic and clinical features of all participants

	n= 36		
Measure	n	Range	Mean – SD or %
Age (yr)	36	(18-50)	36.5–9.6
Education (yr)	36	(11-24)	14.3–2.4
Female	24	66.7%	
Male	12	33.3%	
Axis V			
Current Level	36	(45-70)	55.7–4.7
Highest Level	36	(5-80)	62.8 – 11.8
Age at onset (yr)	35	(8-49)	26.2 – 12.1
Number of episodes	30[a]	(1-4)	1.8 – 1.0
Length of illness (yr)	35	(0-38)	10.1 – 10.5
Length of current episode (months)	36	(1-168)	37.4 – 38.0
Depressive symptom severity			
HRS-D	36	(16-29)	21.2 – 2.7
IDS-C	36	(27-58)	38.1 – 8.0
IDS-SR	33	(28-61)	42.3 – 8.4
Course of illness			
Recurrent, complete recovery	8		22.2%
Recurrent, incomplete recovery	8		22.2%
Single episode	16		44.4%
Unknown	4		11.1%
Depressive subtype (MDD only)			
RDC Primary	30		83.3%
RDC Secondary	4		11.1%
Unknown	2		5.6%
RDC Endogenous	16		44.4%
RDC Nonendogenous	19		52.8%
Unknown	1		2.8%
DSM-IV Meloncholic	8		22.2%
DSM-IV Nonmeloncholic	28		77.8%
Family history subtype			
Depression Spectrum Disease	12		33.3%
Familial Pure Depressive Disease	5		13.9%
Sporadic Depressive Disorder	6		16.7%
Familial Bipolar Disease	1		2.8%
Unknown	12		33.3%

[a]Number of episodes too many to count in n= 6

Polysomnographic Evaluations

Sleep assessments were conducted over two consecutive nights at each measurement occasion in the Department of Psychiatry Sleep Study Unit of the University of Texas Southwestern Medical Center. Night 1 served as a laboratory adaptation night. All PSG and quantitative EEG data reported in the present study are based on Night 2 recordings at each visit. Regular sleep-wake habits were established in advance and confirmed by a self-reported 5-day sleep diary. Alcohol and napping were proscribed and caffeine restrictions were in place during the week of study. Each subject maintained individualized, regular bed and rise times for at least the 5 days prior to sleep study (as confirmed by home diary). An identical sleep-wake schedule was followed during the sleep laboratory studies.

Electroencephalographic (EEG) data were recorded from left (C3) and right (C4) central electrodes with a common ear reference passed through a 10k ohm resistor to minimize nonhomogenous current flow (45). Monopolar, left and right electrooculograms, and bipolar chin-cheek electromyograms were also recorded. A full electrode montage, used on the first night in the sleep laboratory, included leg, chest and abdomen leads, and a nasal-oral thermistor to rule out independent sleep disorders. Interelectrode impedance was maintained below 2 Kohms.

All electrophysiologic signals were recorded on GRASS P-511 A/C amplifiers and displayed on a paperless polygraph system designed and validated in-house. An amplifier sensitivity of 5 was used for EEG (50 V, 0.5-second duration calibration) corresponding to a gain of 50,000, with half-amp low- and high-bandpass filters set at 0.3 and 30 Hz, respectively. A 60-Hz notch filter attenuated electrical noise. Amplifiers were calibrated before and after each night s sleep. As is standard procedure in our laboratory, EEG amplifiers were counterbalanced between hemispheres, across subjects, and between nights to rule out amplifier artifact as a contributing source to interhemispheric differences (46).

Signals were digitized on-line at 250 Hz (62.5 Hz for EOG and EMG) through a 16-bit MICROSTAR analogueto-digital (A/D) converter Raw digitized data were stored on a write-once-read-many (WORM) optical disk for off-line PAA and PSA. Sleep records were scored according to standard analysis criteria (47) by research personnel trained at better than 90% stage agreement on an epoch-by-epoch basis. All records were inspected visually and epochs containing movement, breathing or muscle artifact, or recording difficulties were excluded from analysis.

Computer Quantification of EEG

Period amplitude analysis (PAA) was used to quantify EEG frequency bands. The PAA algorithm used here has been described in detail elsewhere (14,48), and includes zero-cross and first-derivative analyses measuring incidence and an amplitude measure for each frequency band defined as: delta (0.5 to < 4 Hz); theta (4 to < 8 Hz); alpha (8 to < 12 Hz); sigma (12 to < 16 Hz); and beta (16 - 32 Hz).

Briefly, a half-wave zero-cross event is a polarity change in signal voltage between two successive data points. The full-wave first-derivative analysis detects voltage shifts that do not necessarily change polarity, a negative inflection in three successive data points, representing an instance of zero slope. For zero-cross and first-derivative analyses, the algorithm computes the time interval between successive events, thereby determining the frequency. At the end of each 30s epoch, the percentage of total time in each frequency band is computed independently for zero-cross and first-derivative measures. An amplitude measure is derived for each frequency, based on the sum of the squared amplitude of the data points in corresponding zero-cross bins.

Statistical Procedures

The incidence and amplitude measures were averaged in each REM and NREM sleep stage for each subject. Epochs of wakefulness or those with artifact were excluded from analyses. Data were coded for sex (between-group variables), treatment status (baseline, week 5, week 10), hemisphere, sleep stage and EEG frequency band (all within-subject variables). Two overall MANOVAs were computed, one for amplitude and one for incidence. This procedure was used to reduce the complexity of subsequent data analyses, eliminate redundant variables and add statistical rigor against Type I errors.

The MANOVAs indicated that treatment effects did interact with EEG frequency band for amplitude and incidence (F= 2.6, df= 8,27, p<.03; F= 3.4, df= 8,27, p<.009; respectively) but not with hemisphere or sleep stage. Thus, for all subsequent analyses, data were collapsed across sleep stage and hemisphere. Treatment status and EEG frequency band were treated as repeated measures with sex as the between-group variable. The Results Section summarizes the effects of fluoxetine on EEG frequencies for all participants followed by a comparison of study completers versus those who discontinued early. All statistical analyses were conducted using SAS® for Windows routines and conservative Geiser-Greenhouse adjusted probabilities are reported for all effects to further minimize Type I errors.

RESULTS

Sleep Macroarchitecture

Sleep macroarchitectural measures at baseline, week 5 and week 10 are shown in Table 2 for comparison purposes only (see Trivedi et al. for additional detail) (32). Both five and ten weeks of fluoxetine treatment were associated with more disturbed sleep compared to baseline as evidenced by decreased sleep efficiency and % Stages 3 and 4 sleep, and by increased Stage 1 sleep. Latency to the first REM period was significantly longer on treatment with a reduction of 2-4% REM sleep time.

Table 2. Means and standard deviations of key sleep macroarchitectural measures for all participants (n = 36)

	Baseline Mean – S.D	Week 5 on Fluoxetine Mean – S.D	Week 10 on Fluoxetine Mean – S.D
Total Sleep Period (min)	420.3 – 59.9	424.0 – 53.5	419.5 – 54.5
Sleep Latency (min)	17.9 – 10.2	15.3 – 9.1	15.7 – 13.4
REM Latency (min)	80.1 – 25.1	141.6 – 59.5	133.2 – 54.8
% Stage 1	16.4 – 6.3	23.9 – 8.6	24.7 – 8.7
% Stage 2	53.1 – 9.9	51.5 – 8.8	48.4 – 10.9
% Stage 3 + 4	3.2 – 4.4	1.9 – 2.4	1.9 – 2.6
% REM	16.9 – 4.4	12.6 – 4.5	14.5 – 4.5
% Sleep Efficiency	72.5 – 9.0	65.1 – 9.8	64.3 – 10.5

Numbers in boldface are significantly different from baseline p<.05.

Sleep Microarchitecture

Repeated-measures ANOVA revealed significant treatment by EEG frequency band interactions for both amplitude and incidence (F= 4.7, df= 8,272, p<.01; F= 2.8, df= 8,272, p<.05; respectively). To compare treatment effects on individual EEG frequency bands, ANOVAs were computed contrasting baseline to week 5 and baseline to week 10. As predicted, both beta and delta amplitude showed significant changes from baseline at week 5 (F= 8.9, df= 1,34, p<.006; F= 10.3, df= 1,34, p<.003; respectively). The means, shown in Table 3, indicated that beta amplitude increased on fluoxetine, whereas delta amplitude decreased. Comparison between baseline and week 10 was also significant for both beta and delta amplitude (F= 9.2, df= 1,34, p<.005; F= 4.3, df= 1,34, p<.05; respectively). As seen at week 5, beta amplitude was higher after 10 weeks of treatment. Delta amplitude, however, increased from week 5 to week 10, indicating some adaptation over the course of treatment, although still below baseline levels.

Table 3. Means and standard deviations of amplitude and incidence measures at baseline, week 5 and week 10 for all participants (n = 36)

	Baseline	Week 5 on Fluoxetine	Week 10 on Fluoxetine
Amplitude (in V^2)			
Beta	24.2 – 20.0	47.3 – 48.9	46.6 – 53.4
Sigma	20.4 – 8.6	25.4 – 11.1	23.1 – 8.2
Alpha	45.0 – 14.6	50.5 – 16.0	46.9 – 14.9
Theta	125.2 – 38.6	126.9 – 46.2	117.6 – 35.5
Delta	558.5 – 210.7	482.9 – 168.9	526.6 – 229.2
Incidence (% time)			
Beta	29.4 – 13.7	31.3 – 14.4	32.2 – 13.4
Sigma	7.6 – 2.1	8.2 – 2.3	8.1 – 2.2
Alpha	12.8 – 2.9	13.6 – 2.6	12.8 – 2.7
Theta	21.8 – 3.7	21.7 – 4.0	20.7 – 3.7
Delta	53.0 – 9.5	47.2 – 10.5	49.4 – 8.9

Numbers in boldface are significantly different from baseline p<.05.

Interestingly, significant treatment effects were also evident for sigma and alpha amplitude, comparing baseline to week 5 (F= 9.4, df= 1,34, p<.005; F= 9.1; respectively), although these effects were not predicted a priori. Comparing baseline to week 10, only sigma amplitude remained significant (F= 4.9, df= 1,34, p<04). The effect sizes, however, were substantially smaller than that observed for either beta or delta amplitude. Those, in contrast to robust and sustained changes in beta amplitude at both week 5 and week 10, sigma, alpha and delta amplitude showed some adaptation or recovery over the course of treatment. Theta amplitude showed no significant treatment effects (see Table 3).

No treatment effects were evident for incidence measures except for delta. Delta incidence was significantly lower at both weeks 5 and 10 compared to baseline (F= 9.6, df= 1,34; p<.004; F= 6.2, df= 1,34, p<.02; respectively).

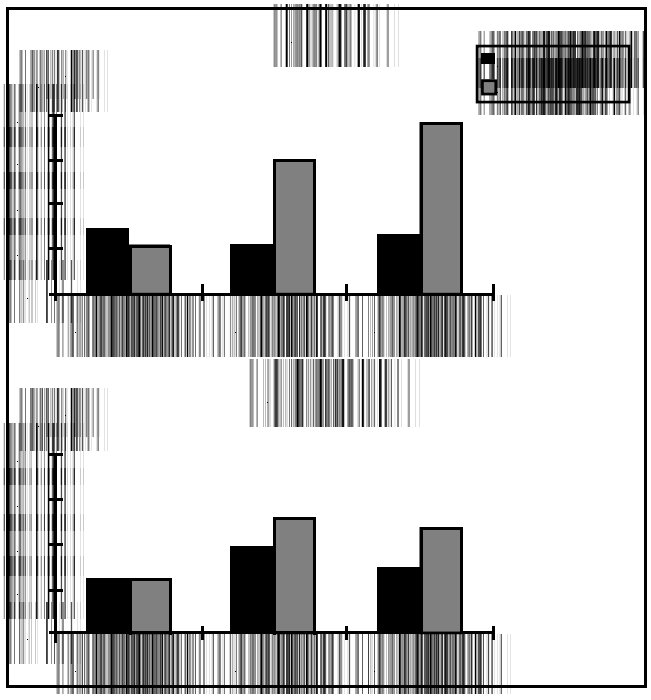
Sex main effects were obtained on a number of EEG measures, but they did not interact with treatment status (F<1) and are, therefore, not reported.

Study Completers Versus Dropouts

Analyses also compared the acute phase effects of fluoxetine on amplitude and incidence measures in those who completed the entire 30 week study versus those who discontinued early to evaluate potential outcome prediction. Of the 36 acute-phase (week 10) treatment responders, 14 dropped out of study prior to week 30. An additional eight patients relapsed during continuation treatment. One additional subject discontinued for unknown reasons and could not be located for follow-up. Thus, 13 participants (5 men and 8 women) completed all phases of the protocol including discontinuation with 23 drop-outs (7 men and 16 women). It is important to note that analyses of the sleep macroarchitectural measures and blood levels of fluoxetine and its metabolites did not differ between study completers and dropouts. However, the HRS-D scores at the end of week 10 were significantly lower (p<.04) in the 13 completers (4.0 – 2.2) compared to drop-outs (6.0 – 2.7) as reported previously (32). Sleep EEG data were coded for group (completers versus dropouts). Treatment status (baseline, week 5 and week 10) was treated as a repeated measure. For this last set of analyses, only beta and delta amplitude and incidence were included.

Results indicated that increased beta amplitude and incidence were evident in study dropouts. The ANOVAs showed a significant treatment status by group interaction for beta incidence (F= 4.4, df= 1,34, p<.04 baseline to week 5; F= 4.4, df= 1,34, p<.04 baseline to week 10). Means indicated higher beta incidence among study dropouts. The interaction for beta amplitude approached significance (F= 2.7, df= 1,34, p<.11 baseline to week 5; F= 3.9, df-1,34, p<.06 baseline to week 10). Means indicated a higher beta amplitude in those who did not complete the study. These effects are also illustrated separately for men and women in Figure 1. Although there was no significant interaction with sex (F= 2.2, df= 3,32, p<.11), the means clearly indicated a greater increase in beta amplitude in male dropouts, as seen in Figure 1. Although fluoxetine decreased delta amplitude and incidence as reported above, differences in delta between completers and dropouts did not approach significance (p<.20).

Figure 1. Mean beta amplitude at baseline, week 5 and week 10 for study completers (n=13) and dropouts (n=23), shown separately for men and women. Five men and 8 women completed all phases of study. Seven men and 16 women dropped out before week 30.



DISCUSSION

As reported for sleep macroarchitecture (32), fluoxetine was alerting to quantitative sleep EEG frequencies. Both the amplitude and incidence of fast-frequency beta activity increased significantly at five and ten weeks of treatment, as hypothesized. Further, delta incidence and amplitude decreased with fluoxetine. Adaptation effects were, however, evident in delta amplitude, with some recovery by the tenth week of treatment. Nevertheless, results indicated that fluoxetine shifted sleep EEG activity to higher frequencies.

In comparing study completers to those who dropped out, patients with the largest fluoxetine-induced EEG changes (from baseline to week 10) were most likely to drop out of study. Those who dropped out had highest beta amplitude and incidence at both week 5 and week 10, although these effects only approached significance.

Our prediction that women would show greater effects of fluoxetine on quantitative sleep EEG frequencies was not confirmed as no sex by treatment interactions were found. In addition, significant differences between study completers and dropouts were evident among men but not women. Men who completed study showed little increase in beta amplitude at either week 5 or week 10, whereas men who dropped out showed three to four times higher beta amplitude on fluoxetine. Women who dropped out also showed higher beta amplitude on fluoxetine compared to women study completers but substantially below that observed in the men who failed to complete the study. We have reported previously that women are more likely than men to be subjectively aware of the alerting effects of fluoxetine (36). Thus, one would expect that the increased subjective awareness of the alerting effects of fluoxetine to be associated with more fast-frequency EEG activity, particularly in those who drop out. Clearly, however, it was men, not women, dropouts who had elevated beta activity. Note that among study completers, women did show more beta activity than men although this difference was not statistically significant. Taken together with other published reports, it appears that the effects of fluoxetine on objective sleep measures are not always in the same direction as subjective effects (28,32,36).

The present study is, however, limited by the sample size of those who completed the full protocol. Thus, the comparisons of EEG differences in completers versus dropouts is best viewed as preliminary, particularly with regard to the sex differences. Nevertheless, the results do indicate that the more fluoxetine increases fast-frequency activity during sleep, the more likely patients are to discontinue treatment. In addition, those with highest amounts of beta activity showed less of a reduction in symptom severity.

Previous work has also suggested that quantitative sleep EEG predicts clinical response to antidepressants (51). In this study, Luthringer et al. demonstrated increased delta activity with a reduction in faster frequency activity in treatment responders. Non-responders showed an EEG profile that included more beta and alpha activity (51). This outcome is in keeping with the findings of the present study that higher amounts of fast-frequency activity were evident in study dropouts.

The effects of fluoxetine on EEG frequencies also fits the profile of several other antidepressants and hypnotic agents such as benzodiazepines, all of which have been shown to shift sleep EEG activity to faster frequencies and to reduce amplitude (38,49). Thus, the apparent paradoxical finding of improved subjective sleep in the presence of elevated fast beta activity is not unique to fluoxetine or SSRIs in general. Notable exceptions include trazodone and some tricyclic antidepressants which have been shown to enhance slow-frequency activity (50) and monoamine oxidase inhibitors (51). Drugs that increase delta activity are, however, typically associated with increased sedation. It would be of interest to evaluate the effects of SSRIs plus trazodone on sleep EEG, since this combination of pharmacotherapy is quite common (52). Theoretically, this combination should be less alerting to both objective sleep macroarchitecture and EEG frequencies. The results of such a study may also be of use in response prediction or in determining who is more likely to complete longer-term antidepressant trials.

In conclusion, fluoxetine increased fast-frequency EEG activity and decreased delta. The increase in beta incidence and amplitude was greatest in those patients who dropped out of study before the end of week 30. These findings suggest that the magnitude of acute-phase treatment effects on quantitative EEG predicts who are likely to remain in study and who will discontinue early. Although it is not feasible to conduct a sleep study on all patients, quantitative sleep EEG data are nevertheless relevant to clinical outcome and is in keeping with the alerting effects of fluoxetine on sleep reported by many patients with depression.

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