Effects of Fluvoxamine and Paroxetine on Sleep Structure in Normal Subjects: A Home-Based Nightcap Evaluation During Drug Administration and Withdrawal

Rosalia Silvestri, M.D.; Edward F. Pace-Schott, M.S., M.A.; Tamara Gersh, B.A.; Robert Stickgold, Ph.D.; Carl Salzman, M.D.; and J. Allan Hobson, M.D.

Background: Acute and chronic administration of the selective serotonin reuptake inhibitors (SSRIs) have been widely reported to disrupt sleep in laboratory studies. This study examines the naturalistic, longitudinal effects of paroxetine and fluvoxamine on sleep quality in the home setting.

Method: Fourteen healthy volunteers free of medical and neuropsychiatric symptoms entered a 31-day protocol: 7 days of drug-free baseline (days 1–7), 19 days of drug treatment (steady state during days 18–26), and 5 days of acute withdrawal (days 27–31). On day 8, the subjects were randomly assigned to receive either 100 mg/day of fluvoxamine or 20 mg/day of paroxetine (half receiving each drug) in divided morning and evening oral doses. Investigators remained blinded to drug assignment until all sleep data had been analyzed. Sleep was monitored using the Nightcap ambulatory sleep monitor. Four standard and 3 novel measures were computed and compared using multivariate analysis of variance, analysis of variance, and Bonferroni-corrected comparison of means.

Results: Sleep disruption was most clearly demonstrated using the novel measures eyelid quiescence index, rhythmicity, and eyelid movements per minute in non–rapid eye movement sleep, but was also apparent as determined by standard measures of sleep efficiency, number of awakenings, and sleep onset latency. Paroxetine disrupted sleep more than fluvoxamine, and paroxetine-induced sleep disruption persisted into the withdrawal phase. Rapid eye movement sleep was suppressed during treatment (especially for fluvoxamine) and rebounded during withdrawal (especially for paroxetine).

Conclusion: We confirm laboratory polysomnographic findings of SSRI-induced sleep quality changes and demonstrate the Nightcap's efficacy as an inexpensive longitudinal monitor for objective sleep changes induced by psychotropic medication.

(J Clin Psychiatry 2001;62:642–652)

Received Sept. 20, 2000; accepted Feb. 1, 2001. From the Laboratory of Neurophysiology (Drs. Stickgold and Hobson and Mr. Pace-Schott) and the Psychopharmacology Program (Drs. Salzman and Ms. Gersh), Massachusetts Mental Health Center, Department of Psychiatry and the Department of Neurology, Brigham and Women's Hospital (Dr. Silvestri), Harvard Medical School, Boston, Mass.

Supported in part by grant RO1-DA11744-01A1 from the National Institute on Drug Abuse (Dr. Hobson), Solvay Pharmaceuticals (Dr. Salzman), the MacArthur Foundation Mind Body Network, and grants MH48832, MH13923, and MH01287 from the National Institutes of Health (Dr. Hobson).

Financial disclosure: Dr. Salzman has served on the speakers/advisory board for SmithKline Beecham. Harvard University holds the patent to the Nightcap ambulatory sleep monitor and has licensed its production to Respironics, Inc. of Pittsburgh, Pa. The Harvard University Laboratory of Neurophysiology will receive a small royalty on sales of the Nightcap when it is brought to the market by Respironics.

The authors thank Theodore P. Cross, Ph.D., for statistical consultation; Roar Fosse, Ph.D., David Kahn, Ph.D., and Matthew Walker, Ph.D., for comments on the manuscript; and Dawn Opstad, M.A., Sarah Marcus, B.A., and Dorothea Abbott, B.A., for logistical support.

Reprint requests to: Edward F. Pace-Schott, M.S., M.A., Laboratory of Neurophysiology, Department of Psychiatry, Harvard Medical School, Massachusetts Mental Health Center, 74 Fenwood Rd., Boston, MA 02115 (e-mail: edward_schott@hms.harvard.edu).

This study examines the longitudinal effects of paroxetine and fluvoxamine on sleep quality in healthy subjects in their natural sleep environment to both increase clinical knowledge of these agents and test an important new methodology for inexpensively monitoring objective sleep changes induced by psychotropic medication. It is well known that depression is commonly associated with consistent sleep alterations involving rapid eye movement (REM) latency (considered as a state and trait marker), increased REM density and number of arousals, and reduced slow-wave sleep. REM suppression is usually considered a sign of treatment efficacy with antidepressant medications and augurs a good response to such treatment.

The high rate of side effects and cardiac complications associated with the tricyclic antidepressant medications, especially in elderly people, has led to the development of less toxic drugs such as the selective serotonin reuptake inhibitors (SSRIs). These compounds are characterized by decreased anticholinergic properties but are still powerful REM sleep suppressants.[1–3] Unfortunately, the SSRIs disrupt sleep even more than their predecessors[4,5] due to their alerting properties[2] via serotonergic enhancement. For a recent review, see Oberndorfer et al.[5]

In addition to REM suppression, sleep disturbances associated with SSRI treatment include the following: insomnia[5]; increased nighttime waking[6,7]; lightening of non-REM (NREM) sleep (including increased proportion of stage 1 NREM relative to stage 2[8] and possibly to stages 3 and 4[1]); oculomotor abnormalities[9,10] (which may persist for over 1 year after drug discontinuation[11]); and an abnormally elevated electromyogram with increased risk of sleep-related movement disorders[12] including REM behavior disorder.[10] Additional sleep disruption is reported during acute withdrawal from such short–half-life SSRIs as fluvoxamine and paroxetine.[13]

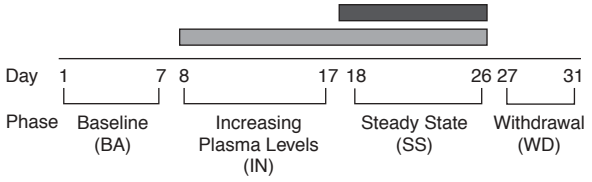
To further explore—and explain—the sleep-disruptive effects of SSRIs, we studied the effects of systematic administration of and withdrawal from paroxetine or fluvoxamine in healthy adult volunteers. We took advantage of our novel home-based recording system, the Nightcap, to realize a longitudinal repeated-measures protocol that matched the conditions of clinical treatment trials in a much more cost-effective manner than could be achieved in the sleep laboratory. This is the first study to demonstrate that the Nightcap system can quantitate drug effects on sleep and that some of its measures may even exceed the sensitivity of traditional sleep laboratory techniques.

METHOD

Participants

Participants were 14 healthy paid volunteers (4 men, 10 women; mean age = 27.4 years [range, 22–39 years]) recruited by newspaper advertisements. Participants were determined to be free of medical and neuropsychiatric symptoms or treatment with (or abuse of) psychotropic or sleep-affecting drugs via an extensive telephone screening that included many questions drawn from traditional instruments such as the Structured Clinical Interview for DSM-IV and that was then followed by an unstructured, in-person interview with a psychiatrist. Subjects gave written informed consent after the study protocol and possible side effects were fully explained. Subjects were randomly assigned to receive either fluvoxamine or paroxetine (half receiving each drug), and investigators remained blind as to which subject received which drug until all sleep data had been collected. (Subjects were not told which of the 2 drugs listed on the informed consent form they were to be given, and no information was provided on any expected differences between the 2 drugs; however, subjects could have determined which of the 2 drugs they were taking since the pills were given in their commercial form.) All participants denied current substance abuse and agreed, during the study, to refrain from taking any sleep-affecting or recreational drugs and to clear all needed medication with an investigator. Moderate amounts of alcohol and caffeine were allowed; most participants were nonsmokers, and the only drugs reported used during the study (via daily written query) were non–sleep-affecting analgesics (e.g., ibuprofen).

Figure 1. Experimental Design of Study[a]



[a]The phases of the study were defined as follows: BA, days 1–7; IN, days 8–17; SS, days 18–26; WD, days 27–31. The upper bar identifies the steady-state study phase, whereas the lower bar illustrates the entire drug treatment period.

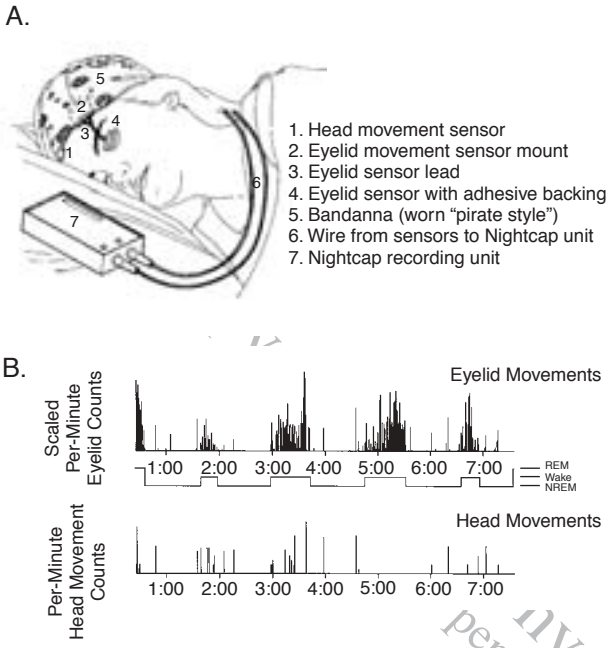
Procedure

The study lasted 31 days and consisted of 7 days of baseline, 19 days of either 100 mg/day of fluvoxamine or 20 mg/day of paroxetine (given in divided morning and evening oral doses), and 5 days of acute withdrawal. Dosing was begun on day 8, and steady-state levels were considered to be well achieved after 10 days of treatment (day 18) on the basis of the assumption that 5 half-lives are required to achieve steady state.[14] This experimental design is illustrated in Figure 1. Subjects' sleep was monitored using the Nightcap ambulatory sleep monitor,[15] which was worn nightly during baseline, initial dosing, and withdrawal and every third night between days 12 and 26. Nightcap recordings were obtained on 7 days during baseline (BA, days 1–7), on 3 days during the time when steady-state plasma levels were achieved (SS, days 20, 23, and 26), and on 5 days during withdrawal (WD, days 27–31). Therefore, there were a maximum of 7 BA , 3 SS, and 5 WD nights of data potentially gathered for each subject. (A few subjects wore the Nightcap for additional SS or BA nights, the data from which were then included in the calculation of mean sleep parameter values for each study phase as described below.) Although a total of 6 Nightcap recordings were obtained during the initial nights of drug dosing (days 8–11) and the period of increasing plasma drug levels (days 14 and 17), these recordings were not analyzed in the current study because steady plasma levels of drug could not be assumed to be present over these periods.

The Nightcap Ambulatory Sleep Monitor

The Nightcap is a 2-channel recording device that distinguishes wake, REM sleep, and NREM sleep.[15] One channel of the Nightcap monitors eye movement, and the other monitors major head movements (Figure 2). The Nightcap analyzer (NC Analyzer) software[15] uses raw per-minute eyelid and head movement counts and a computerized algorithm to score each recorded minute as wake or REM or NREM sleep. The per-minute agreement of the

Figure 2. The Nightcap Ambulatory Sleep Monitor. (A) Photo-Based Drawing of the Nightcap and Its Mode of Attachment Using a Bandanna and (B) Nightcap-Derived Record of a Good Sleeper Displayed Graphically[a]



[a]Reprinted, with permission, from Ajilore et al.[15] Abbreviations: NREM = non–rapid eye movement, REM = rapid eye movement. Times shown in x axis designate time of night/morning. The top graph is a histogram of eyelid movements per minute displayed over the Nightcap's clock time. The middle graph shows the hypnogram algorithmically computed by NC Analyzer software.[15] The bottom graph is a histogram of head movements per minute displayed over the Nightcap's clock time.

Nightcap with polysomnographic scoring of these same 3 stages is 87%.[15] For further details on the Nightcap hardware and the NC Analyzer software, see reference 15.

Analysis of Data

Three main study phases were defined as described above in the Procedure section. Nightcap records were discarded if they showed any identifiable artifact (e.g., mid-recording cessation of eyelid sensor signal, indicating breakage) or if a subject reported problems (e.g., subject-reported sensor breakage). Sleep parameters computed from Nightcap data and compared among the 3 study phases included (1) 4 traditional sleep quality indices: sleep efficiency (SE), number of awakenings (AWAKE), sleep onset latency (SOL), and percent NREM sleep (%NREM); (2) 3 novel Nightcap-based sleep quality parameters; eyelid quiescence index (EQI), rhythmicity (RHYTHM), and eyelid movements per minute in NREM (ELM/MIN NREM); and (3) 2 measures specifically related to REM processes: eyelid movements per minute in REM (ELM/MIN REM) and REM latency (RLAT). Participants' subjective perception of the quality of their sleep and immediate postwaking state of mind were assessed via a questionnaire completed every morning of the study on awakening. Each of these parameters is described in more detail in the next section. Mean values for each parameter, for each subject, in each study phase were the raw data entered into subsequent analyses.

The mean per-subject values for each parameter for each study phase constituted 3 repeated measures in 2-way (study phase × drug) repeated-measures multivariate analyses of variance (MANOVAs) and univariate analyses of variance (ANOVAs) that were performed, respectively, on sleep parameters grouped by physiologic category and on each sleep parameter individually. Mean values were compared between study phases only when the univariate ANOVA showed significant variation ($p < .05$) of the parameter being analyzed associated with the repeated measure (i.e., study phase). The alpha level used for comparison of means ($p < .0167$) was Bonferroni-adjusted for increased probability of type I error in 3 multiple comparisons (BA vs. SS, BA vs. WD, SS vs. WD).

Since initial differences existed between the 2 drug groups with regard to sleep quality variables (i.e., at baseline; see Results), the sleep quality effects of the 2 drugs were compared using the following 2 methods: (1) First, between-group comparisons were made for data gathered during the steady-state and withdrawal phases by repeated-measures analysis of covariance (ANCOVA) using subjects' baseline value for each sleep parameter as covariates. (2) Second, repeated-measures ANOVAs were computed for the 3 study phases for each drug group individually (i.e., in each ANOVA, N = 7).

ANOVA and comparisons of means were computed using Super Anova for the Macintosh (Abacus Concepts, Inc., Berkeley, Calif.), and MANOVA and ANCOVA comparisons were computed using Statistical Package for the Social Sciences, Inc. (SPSS Inc., Chicago, Ill.) software.

Nightcap- and Questionnaire-Derived Sleep Parameters

Sleep efficiency (SE) was defined as the number of Nightcap-scored minutes of sleep (REM and NREM), divided by total number of minutes in bed, times 100. A higher sleep efficiency is indicative of better-quality sleep.

Number of awakenings (AWAKE) refers to the number of macroarousals detected by the Nightcap. A lower number of awakenings is indicative of better-quality sleep.

Sleep onset latency (SOL) refers to the judge-determined estimates of the number of minutes from sleep onset to the first minute of NREM sleep. Scorings were performed on randomized Nightcap records for which judges were blind to subject identity, drug, and study phase. A lower sleep onset latency is indicative of better-quality sleep.

Percent NREM sleep (%NREM) was defined as the total number of minutes scored as NREM sleep, divided by the total number of minutes in bed, times 100. It is well

accepted that age-appropriate amounts of slow-wave sleep are associated with good sleep quality. One of the most well-documented effects of the SSRI fluoxetine is its tendency to lighten sleep, which is most often seen as an increase in the number of awakenings and the percentage of stage 1 NREM sleep at the expense of deeper NREM and REM sleep.[1,6–8] For this reason, we hypothesized that SSRI-associated sleep disturbance might be indexed by a decrease in the overall percentage of Nightcap-scored NREM sleep, which the Nightcap's scoring algorithm recognizes as periods of low eyelid and body motility.

Eyelid quiescence index (EQI) was defined as the total number of minutes during the total time in bed in which the Nightcap eyelid channel detected no above-threshold[15] eyelid movements, divided by total sleep duration in minutes, times 100.[16]

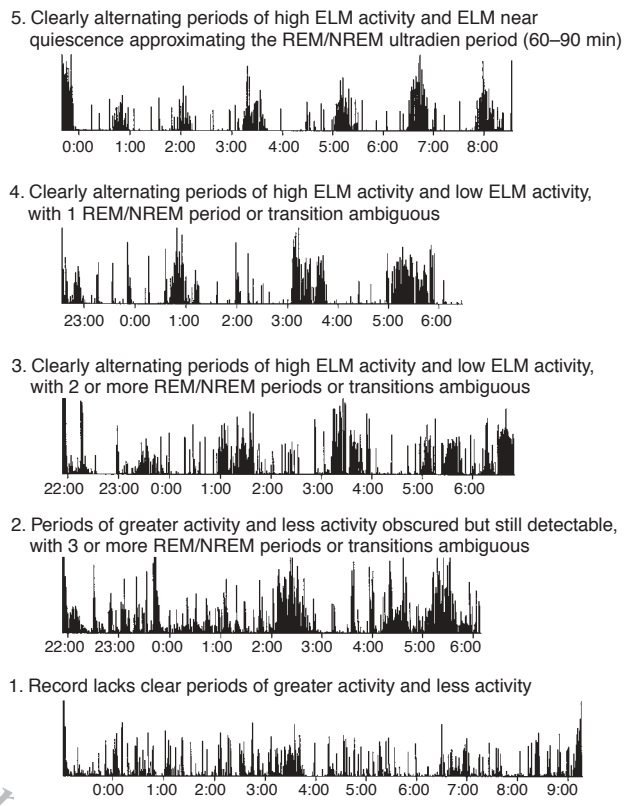
Rhythmicity (RHYTHM) refers to the judge-determined assignments, on a standardized 1-to-5 scale, of the regularity and stage segregation of a night's REM-NREM alternation as well as its overall sleep consolidation (Figure 3). Rhythmicity scores used in analyses were the means of scores by 3 judges who were blind to subject, study phase, and drug. Intraclass correlation analyses of the 3 judges' scores for mean rhythmicity within each study phase among the 14 subjects demonstrated an acceptable rate of agreement (BA, 0.84; SS, 0.58; WD, 0.78). A higher rhythmicity score is indicative of better-quality sleep.

Eyelid movements per minute in NREM (ELM/MIN NREM) and *eyelid movements per minute in REM* (ELM/MIN REM) were defined as a night's average number of above-threshold eyelid movements in each minute algorithmically scored as either NREM sleep or REM sleep, respectively. While EQI gives a measure of eyelid quiescence over the entire night, with higher measures indicative of better sleep quality, ELM/MIN NREM gives a measure of eyelid motility (i.e., the opposite of quiescence) in NREM sleep, with lower values indicative of better sleep quality.

REM latency (RLAT) refers to the judge-determined estimates of the number of minutes from sleep onset to the first minute of REM sleep. Scorings were performed on randomized Nightcap records for which judges were blind to subject identity, drug, and study phase. Lower RLAT is indicative of greater physiologic pressure to enter REM from the initial NREM sleep following sleep onset.[2]

Subjective sleep quality was measured by a questionnaire which consisted of 4 Likert scales that asked subjects to rate "your overall quality of sleep," "how deeply you slept," "how well rested you felt when you got up," and "how mentally alert you felt when you got up" on a 1-to-5 scale, with 1 representing best quality. In addition, 3 yes/no questions assessed difficulties with sleep onset ("had a hard time getting to sleep"), sleep maintenance ("woke up more frequently than usual"), or early awakening ("woke earlier than your usual time").

Figure 3. Scoring Rules and Examples for the 5-Point Rhythmicity Scale[a]



[a]Abbreviations: ELM = eyelid movements, NREM = non–rapid eye movement, REM = rapid eye movement. Times shown in x axis designate time of Nightcap recording. Rules and examples determined by judges viewing nightly Nightcap records displayed by the NC Analyzer software.[15]

Grouping of Sleep Parameters for MANOVA

Four groupings of the above Nightcap-derived parameters were analyzed for study phase and drug main effects and interactions using MANOVA. Groupings included all sleep quality indices (SE , AWAKE, SOL, %NREM, EQI, RHYTHM, ELM/MIN NREM), traditional sleep quality indices alone (SE, AWAKE, SOL, %NREM), novel sleep quality indices alone (EQI, RHYTHM, ELM/MIN NREM), NREM-related sleep quality indices (%NREM, ELM/MIN NREM), and REM-sleep–related indices (ELM/MIN REM, RLAT).

RESULTS

General Characteristics of Nightcap Recordings Over All Study Phases

Among the 14 subjects, usable Nightcap recordings were obtained from 4 to 8 BA nights (mean = 5.79 recordings), from 1 to 6 SS nights (mean = 2.93 recordings, with most subjects producing 2 or 3 and only 1 subject each producing the minimum 1 and maximum 6), and from 3 to 5

acute WD nights (mean = 4.14 recordings). To rule out any systematic bias introduced into study phase mean values by instability of data within a study phase, we performed repeated-measures ANOVAs for each variable in a subset of subjects for whom we had usable data for all 3 possible SS nights (N = 10) and a subset of subjects for whom we had usable data for at least 4 WD nights including the first WD night (N = 9). In these 14 ANOVAs, the only significant difference across the repeated measures was for EQI during WD ($F = 3.462$, $df = 3,24$; $p = .032$); EQI was significantly greater on the fourth WD night compared with the first ($p = .0089$) and compared with the first 3 nights combined ($p = .0144$), and EQI on the third and fourth WD nights combined was significantly greater than on the first 2 WD nights combined ($p = .0061$). These differences suggest the possibility of poorer sleep quality during the initial compared with later WD nights as measured by EQI alone. Even for EQI, however, it is unlikely that this pattern would have systematically affected the mean scores across the 5-day WD period (which were used in analyses) because data from the first WD night were unusable in only 1 subject and approximately equal numbers of subjects were missing values for the second WD night and later WD nights.

Sleep Quality Changes Over Baseline, Steady State, and Acute Withdrawal Study Phases

SSRI treatment was found to significantly degrade sleep quality as measured using both traditional and novel sleep quality indices analyzed by MANOVA, ANOVA, and post hoc comparison of study phase means. Using MANOVA, the "3 novel sleep quality indices" grouping showed a significant study phase (BA vs. SS vs. WD) Huyunh-Feldt adjusted main effect ($F = 9.662$, $df = 2,21.21$; $p = .001$). The study phase main effect was not significant for the other 3 groupings of sleep quality variables using MANOVA.

ANOVAs computed for each sleep quality variable showed significant study phase main effects for SE, SOL, EQI, RHYTHM, and ELM/MIN NREM, with a trend toward a study phase main effect for AWAKE but no study phase main effect for %NREM (Table 1).

Post hoc means comparisons for study phase showed significantly lower sleep quality during steady-state treatment as compared with predrug baseline for several sleep quality variables (see Table 1). These variables included both the traditional measures SE and SOL (with a trend for AWAKE) as well as the novel measures EQI, RHYTHM, and ELM/MIN NREM. In the case of AWAKE ($p = .0187$), the difference in mean values showed a medium effect size ($0.50 < \text{effect size} < 0.80$)[17] of 0.70, suggesting that, with a larger sample size, there would be sufficient statistical power to achieve significance.

Post hoc study phase means comparisons showed significantly lower sleep quality in the withdrawal phase compared with baseline for the novel measure EQI (see Table 1). There was also a trend for SOL with a large effect size of 0.90.

Post hoc study phase means comparisons showed significantly lower sleep quality in steady state compared with withdrawal for the novel measures RHYTHM and ELM/MIN NREM (see Table 1), with a trend in the same direction for the traditional measure SE with an almost medium effect size of 0.49, suggesting that there would be sufficient statistical power to achieve significance with a larger sample size.

In no cases did sleep quality improve from baseline to steady state or from baseline to withdrawal, nor did sleep quality ever decrease from steady state to withdrawal. No significant study phase–related differences were seen for any subjective measure of sleep quality or immediate postwaking state of mind.

Differential Effects on Sleep Quality Between Paroxetine and Fluvoxamine

Treatment with paroxetine degraded sleep quality more than did treatment with fluvoxamine. This differential effect was suggested by both types of analyses used to compare the sleep quality effects of the 2 drugs, taking into account baseline group differences (see Method).

ANCOVA. Using univariate ANCOVAs with baseline value as covariate for each of the 7 sleep quality variables, trends toward better sleep quality in fluvoxamine- versus paroxetine-treated patients were seen for EQI ($F = 3.708$; $df = 1,11$; $p = .080$) and %NREM ($F = 3.38$; $df = 1,11$; $p = .093$). These 2 trends showed large (> 0.80) effect sizes[17] (1.14 and 0.91, respectively), suggesting that, with a larger sample size, there would be sufficient statistical power to achieve significance.

Study phase differences within each drug group. The differential sleep effects of the 2 SSRIs were most dramatically illustrated when repeated-measures ANOVAs were carried out on each drug group individually (Table 2).

Among the 7 sleep quality variables in the fluvoxamine group, a significant main effect for the repeated measure (study phase) was seen only for RHYTHM and ELM/MIN NREM. Comparison of study phase means in the fluvoxamine group showed significantly lower sleep quality in steady state compared with baseline and withdrawal for RHYTHM only; trends toward greater ELM/MIN NREM were seen for steady state compared with baseline and withdrawal, both comparisons having medium effect sizes of 0.68 and 0.63, respectively.

In contrast, in the paroxetine group, 5 of 7 sleep quality variables showed a significant main effect for study phase (SE, %NREM, EQI, RHYTHM, and ELM/MIN NREM), while the remaining 2 (AWAKE, SOL) showed a trend toward significance. In the paroxetine group, steady state showed significantly lower sleep quality than baseline for EQI, RHYTHM, ELM/MIN NREM, and SE, as well as

Table 1. Variation in Sleep Quality and REM Sleep by Study Phase (N = 14 subjects)[a]

Measure[b]	Baseline (BA)	Steady State (SS)	Withdrawal (WD)	Main Effect[c]	Post Hoc Comparison[d] BA vs SS	BA vs WD	SS vs WD
Sleep quality							
Traditional							
Sleep efficiency, %	94.89 ± 2.76	87.61 ± 10.75	91.85 ± 5.6	F = 6.608, df = 2,24; p = .0052	BA > SS: F = 13.097, df = 1,24; p = .0014	NS	SS > WD: F = 4.446, df = 1,24; p = .0456
No. of awakenings	1.42 ± 0.54	2.32 ± 1.73	1.78 ± 1.02	F = 3.224, df = 2,24; p = .0575	BA < SS: F = 6.367, df = 1,24; p = .0187	NS	NS
Sleep onset latency, min	12.5 ± 4.7	24.3 ± 15.9	20.4 ± 11.5	F = 5.087, df = 2,24; p = .0144	BA < SS: F = 9.794, df = 1,24; p = .0046	BA < WD: F = 4.403, df = 1,24; p = .0466	NS
% NREM	61.87 ± 6.71	60.03 ± 12.57	57.69 ± 9.69	NS	NS	NS	NS
Novel							
Eyelid quiescence index, %	49.13 ± 7.59	42.11 ± 11.81	43.44 ± 11.07	F = 9.051, df = 2,24; p = .0012	BA > SS: F = 16.039, df = 1,24; p = .0065	BA > WD: F = 10.537, df = 1,24; p = .0034	NS
Rhythmicity, 1–5	3.75 ± 0.48	2.50 ± 0.48	3.53 ± 0.56	F = 57.266, df = 2,24; p = .0001	BA > SS: F = 100.57, df = 1,24; p = .001	NS	SS < WD: F = 68.068, df = 1,24; p = .0001
No. of eyelid movements/min in NREM	3.29 ± 0.65	4.57 ± 1.60	3.39 ± 0.96	F = 22.732, df = 2,24; p = .0001	BA < SS: F = 36.691, df = 1,24; p = .001	NS	SS < WD: F = 31.292, df = 1,24; p = .0001
REM sleep–related							
No. of eyelid movements/min in REM	30.17 ± 6.92	30.72 ± 6.23	36.11 ± 10.53	F = 6.738, df = 2,24; p = .0048	NS	BA < WD: F = 11.037, df = 1,24; p = .0029	SS < WD: F = 9.089, df = 1,24; p = .006
REM latency, min	72.4 ± 19.4	101.5 ± 44.5	72.6 ± 22.5	F = 6.628, df = 2,24; p = .0051	BA < SS: F = 10.023, df = 1,24; p = .0042	NS	SS > WD: F = 9.862, df = 1,24; p = .0044

[a]Abbreviations: NREM = non–rapid eye movement, NS = not significant, REM = rapid eye movement. Repeated-measures analysis of variance (ANOVA) performed with drug (fluvoxamine vs. paroxetine) as the factorial and study phase (BA, SS, WD) as the repeated measure. Differences were considered significant at $p < .05$ for main effects and $p < .0167$ for post hoc means comparisons. Main effects at $p < .1$ and means comparisons at $p < .05$ reported as statistical trends.
[b]Values shown as mean ± SD.
[c]Study phase main effect as determined using univariate ANOVA.
[d]Bonferroni-corrected post hoc means contrasts between study phases.

trends for AWAKE and SOL, which both showed large effect sizes of 1.14 and 0.88, respectively. Steady state showed significantly lower sleep quality than withdrawal for RHYTHM and ELM/MIN NREM, indicating some recovery during withdrawal from treatment-associated sleep disruption. Notably, however, in the case of paroxetine, treatment-induced sleep disruption relative to baseline persisted into withdrawal as shown by significant differences for EQI and %NREM and a trend for RHYTHM (a large effect size of 0.86).

No significant drug-related differences were seen for any subjective measure of sleep quality or immediate post-waking state of mind. There were trends ($p < .1$) for Likert scale–rated overall sleep quality, sleep depth, and morning restedness on awakening (see Method) to reflect poorer sleep with paroxetine (with large effect sizes of 0.89, 0.86, and 0.82, respectively). This trend was not, however, seen in Likert scale scores of morning alertness or for frequency of "yes" responses to yes/no questions on difficulty initiating or maintaining sleep or on early awakening.

Comparison of Novel and Traditional Sleep Quality Measures

Since the Nightcap-based novel measures of sleep quality (EQI, RHYTHM, ELM/MIN NREM) have, to date, been used only preliminarily,[16] simple regressions between Nightcap data–based traditional and novel sleep quality parameters were performed. Study phase means for novel/traditional variable pairs were used, since these were the raw data used in ANOVA comparisons of study phase and drug effects. Regressions were performed separately within each of the 3 study phases. Correlations of novel measures with sleep onset latency were not performed, since this sleep initiation index could be expected

Table 2. Variation in Sleep Quality and REM Sleep by Study Phase for Paroxetine- and Fluvoxamine-Treated Subjects[a]

	Paroxetine (N = 7)						
					Post Hoc Comparison[d]		
Measure[b]	Baseline (BA)	Steady State (SS)	Withdrawal (WD)	Main Effect[c]	BA vs SS	BA vs WD	SS vs WD
Sleep quality							
Traditional							
Sleep efficiency, %	93.91 ± 3.58	83.47 ± 13.78	89.48 ± 6.38	F = 4.355, df = 2,12; p = .0379	BA > SS: F = 8.644, df = 1,12; p = .0124	NS	NS
No. of awakenings	1.56 ± 0.54	2.83 ± 1.48	2.17 ± 1.04	F = 2.957, df = 2,12; p = .0904	BA < SS: F = 5.910, df = 1,12; p = .0317	NS	NS
Sleep onset latency, min	13.2 ± 5.3	23.5 ± 15.6	20.8 ± 12.3	F = 2.918, df = 2,12; p = .0928	BA < SS: F = 5.425, df = 1,12; p = .0381	NS	NS
% NREM	58.30 ± 7.27	52.83 ± 12.89	50.75 ± 8.40	F = 4.288, df = 2,12; p = .0394	NS	BA > WD: F = 8.037, df = 1,12; p = .0150	NS
Novel							
Eyelid quiescence index, %	44.94 ± 7.67	35.13 ± 12.17	34.98 ± 8.80	F = 10.369, df = 2,12; p = .0024	BA > SS: F = 15.322, df = 1,12; p = .0021	BA < WD: F = 15.780, df = 1,12; p = .0019	NS
Rhythmicity, 1–5	3.77 ± 0.58	2.36 ± 0.60	3.29 ± 0.54	F = 30.609, df = 2,12; p = .0001	BA > SS: F = 59.28, df = 1,12; p = .0001	BA > WD: F = 6.992, df = 1,12; p = .0214	SS < WD: F = 25.554, df = 1,12; p = .0003
No. of eyelid movements/min in NREM	3.71 ± 0.36	5.65 ± 1.24	3.89 ± 0.95	F = 19.920, df = 2,12; p = .0002	BA < SS: F = 32.567, df = 1,12; p = .0001	NS	SS > WD: F = 26.927, df = 1,12; p = .0002
REM sleep–related measures							
No. of eyelid movements/min in REM	32.95 ± 3.46	31.32 ± 7.72	41.07 ± 7.63	F = 7.73, df = 2,12; p = .007	NS	BA < WD: F = 9.348, df = 1,12; p = .0099	SS < WD: F = 13.466, df = 1,12; p = .0032
REM latency, min	65.6 ± 12.6	88.2 ± 38.9	73.2 ± 28.4	NS	NS	NS	NS

[a]Abbreviations: NREM = non–rapid eye movement, NS = not significant, REM = rapid eye movement. Repeated-measures analysis of variance performed for each drug group individually, on each sleep quality and REM-related variable, using study phase (BA, SS, WD) as the repeated measure. Differences were considered significant at $p < .05$ for main effects and $p < .0167$ for post hoc means comparisons. Main effects at $p < .1$ and means comparisons at $p < .05$ reported as statistical trends.

to vary independent of the remaining sleep maintenance measures. Low EQI, high ELM/MIN NREM, and low RHYTHM were hypothesized to measure an overall disturbance of sleep maintenance involving microarousals and macroarousals. Such sleep disturbance is also likely to be reflected by the traditional measures of low SE, high AWAKE, and low %NREM.

As can be seen in Table 3, using the Larzelere Mulaik modification of the Bonferroni correction[18] for 27 repeated correlations, EQI correlated significantly with SE in WD and with %NREM in all 3 study phases, whereas RHYTHM correlated significantly with SE in WD. Given the small sample size (N = 14), it is difficult to demonstrate statistical significance with such a correction for repeated testing; however, following the conventions of Cohen,[19] all but 5 of these 27 correlation coefficients represent a large effect size ($r > 0.4$), suggesting that, with a larger sample size, there would be sufficient statistical power to achieve significance. Moreover, all regression line slopes except for the one with the lowest correlation coefficient were in the predicted directions. Therefore, a substantial degree of agreement exists between novel and traditional Nightcap-derived sleep quality measures.

REM-Related Changes Over Baseline, Steady State, and Acute Withdrawal for Paroxetine Versus Fluvoxamine

Paroxetine and fluvoxamine produced significant effects on REM sleep–related variables, suggesting their attenuating effects on REM during steady-state treatment

Fluvoxamine (N = 7)						
Baseline (BA)	Steady State (SS)	Withdrawal (WD)	Main Effect[c]	Post Hoc Comparison[d] BA vs SS	BA vs WD	SS vs WD
95.86 ± 1.20	91.76 ± 5.36	94.22 ± 3.74	NS	NS	NS	NS
1.27 ± 0.54	1.80 ± 1.91	1.39 ± 0.90	NS	NS	NS	NS
11.8 ± 4.4	25.2 ± 17.4	20.1 ± 11.7	NS	NS	NS	NS
65.44 ± 3.85	67.22 ± 7.43	64.63 ± 4.59	NS	NS	NS	NS
53.31 ± 5.01	49.10 ± 6.35	51.90 ± 4.60	NS	NS	NS	NS
3.73 ± 0.40	2.64 ± 0.32	3.77 ± 0.50	F = 28.793, df = 2,12; p = .0001	BA > SS: F = 41.488, df = 1,12; p = .0001	NS	SS < WD: F = 44.828, df = 1,12; p = .0001
2.87 ± 0.61	3.49 ± 1.14	2.89 ± 0.71	F = 3.964, df = 2,12; p = .0477	BA < SS: F = 6.139, df = 1,12; p = .0291	NS	SS > WD: F = 5.747, df = 1,12; p = .0337
27.39 ± 8.57	30.11 ± 4.84	31.14 ± 11.16	NS	NS	NS	NS
85.5 ± 23.4	127.6 ± 52.8	86.4 ± 31.1	F = 4.941, df = 1,12; p = .0272	BA < SS: F = 7.583, df = 1,12; p = .0175	NS	SS > WD: F = 7.234, df = 1,12; p = .0197

[b]Values shown as mean ± SD.
[c]Study phase main effect.
[d]Bonferroni-corrected post hoc means contrasts between study phases for each drug.

and possible REM rebound during withdrawal. MANOVA computed for the "2 REM-related measures" (ELM/MIN REM and RLAT) showed a significant study phase effect ($F = 5.046$, $df = 2,24$; $p = .015$). No drug main effect or study phase × drug interaction was seen for these 2 variables using MANOVA.

ANOVAs computed for the 2 REM-related measures showed a significant study phase main effect for both ELM/MIN REM and RLAT (see Table 1). Post hoc means comparisons for study phase showed significantly higher ELM/MIN REM in WD compared with both BA and SS and significantly higher RLAT in SS compared with BA and WD.

Repeated-measures ANOVAs were also carried out on each drug group individually for the 2 REM-related variables (see Table 2). These comparisons showed a greater treatment-related effect on RLAT for fluvoxamine but a greater withdrawal-related increase in ELM/MIN REM for paroxetine. The fluvoxamine group showed a significant study phase main effect for REM latency, with a trend for RLAT to be greater in SS compared with both BA and WD (with large effect sizes of 1.03 and 0.95, respectively). RLAT was also prolonged during SS in the paroxetine group, but this did not reach a trend or significance. In contrast, the paroxetine group showed a significant study phase main effect for ELM/MIN REM, with significantly greater ELM/MIN REM in WD compared with both BA and SS. In the fluvoxamine group, there was no significant study phase main effect for ELM/MIN REM.

DISCUSSION

The results of this study confirm, in healthy subjects studied at home, previous polysomnographic findings on SSRIs in the sleep laboratory setting,[1,4–7] including:

1. disruptive effects on sleep quality during treatment at the commonly prescribed initial doses of these popular SSRIs,
2. persistence of sleep effects (sleep disruption and/or alteration of REM-related variables) into the withdrawal phase,
3. greater overall sleep disruptive effects of paroxetine compared with fluvoxamine, and
4. treatment-associated REM suppression (especially for fluvoxamine) and withdrawal-associated REM rebound (especially for paroxetine).

SSRI-induced sleep disruption was most clearly demonstrated using 3 novel, Nightcap-based sleep quality measures: (1) EQI, a measure inversely related to the frequency of microarousals especially from NREM sleep; (2) RHYTHM, which estimates the regularity of REM-NREM alternation as well as overall sleep consolidation; and (3) ELM/MIN NREM, a measure hypothesized to reflect suppression of microarousals (and/or sleep depth) during NREM sleep. It is important to note that, since depressed patients are known to have alterations of the serotonin system, the sleep effects of the SSRIs in such individuals may be of an even greater magnitude than those observed in the healthy subjects of the current study.

Our results clearly show a greater overall sleep disruptive effect of paroxetine compared with fluvoxamine for all sleep quality indices. Notably, this Nightcap-measured sleep quality disruption persisted into acute withdrawal with paroxetine but not fluvoxamine. A differential effect of the 2 drugs with regard to their REM-sleep effects was also noted, with fluvoxamine producing a greater treatment-related prolongation of REM latency (hypothesized to reflect REM suppression) while paroxetine produced a greater withdrawal-associated increase in REM-associated eyelid movement density.

Possible Mechanism of Observed Differential Drug Effects

Two possible mechanisms for the greater sleep disruptive effects of paroxetine relative to fluvoxamine include (1) paroxetine's mild anticholinergic properties[20] and/or (2) paroxetine's stronger serotonergic effects, which would activate serotonin-2A/2C receptors, which control slow-wave sleep continuity via negative feedback[4,21] and thus more greatly disrupt NREM sleep. The NREM sleep–related sleep quality indices (%NREM, ELM/MIN NREM) appear to be particularly sensitive to SSRI treatment–related sleep disruption. This conclusion is strengthened by the fact that most nocturnal accumulation of eyelid-quiescent epochs must take place during NREM sleep. Similarly, higher RHYTHM scores depend strongly on the clear separation of successive REM periods by intervening eyelid-quiescent NREM epochs.

It is notable that while fluvoxamine resulted in a greater prolongation of REM latency, it was paroxetine that produced a greater elevation of eyelid movements per minute in REM sleep (ELM/MIN REM) during acute WD. This apparent discrepancy between greater apparent REM suppression effects combined with lesser apparent REM rebound effects in fluvoxamine compared with paroxetine may be explained as follows: The tonic physiologic mechanism of REM latency may be dissociable from the phasic mechanisms underlying actual bursts of REM saccades. For example, elevated ELM/MIN REM in WD for paroxetine may reflect the same underlying mechanism as the continued sleep disturbance in WD seen with this drug, i.e., a prolongation of central nervous system–activating effects into the withdrawal phase.

Table 3. Correlation Coefficients and Simple Regression Analysis of Novel and Traditional Nightcap-Derived Sleep Quality Parameters[a]

	Traditional Measures		
Novel Measure	Sleep Efficiency	No. of Awakenings	% NREM
Eyelid quiescence index			
Baseline	.693	–.691	.874[b]
Steady state	.731	.328	.943[c]
Withdrawal	.754[d]	.236	.906[e]
Eyelid movements/min NREM			
Baseline	–.302	.558	–.740
Steady state	–.715	.714	–.597
Withdrawal	–.606	.507	–.551
Rhythmicity			
Baseline	.433	.044	.542
Steady state	.535	–.368	.551
Withdrawal	.630[f]	–.159	.598

[a]Abbreviations: NREM = non–rapid eye movement, % NREM = percentage of sleep time in NREM sleep. Simple regressions performed using Larzelere Mulaik modification of Bonferroni correction[18] for 27 individual regressions.
[b]F = 38.902, df = 1,13; p < .0001.
[c]F = 95.862, df = 1,13; p < .0001.
[d]F = 15.779, df = 1,13; p = .0019.
[e]F = 54.943, df = 1,13; p < .0001.
[f]F = 7.909, df = 1,13; p = .00157.

Findings on REM Sleep–Related Variables

Data from both drugs combined showed the predicted treatment-related prolongation of RLAT that has been repeatedly reported in polysomnographic studies.[4,8,22,23] This increased RLAT during treatment may be attributable to a serotonergic suppression of cholinergic REM mechanisms.[24,25] We hypothesize that increased ELM/MIN REM during withdrawal reflects increased REM intensity due to rebound from serotonergic REM suppression, a finding also reported in polysomnographic studies.[8]

Advantages and Limitations of Nightcap-Based Measures

To our knowledge, this is one of the first studies comparing the long-term sleep effects of 2 SSRIs with similar pharmacokinetic properties. Previous studies have, instead, compared SSRIs with tricyclics[26,27] or have compared the acute sleep effects of SSRIs of differing half-lives (e.g., reference 28).

The current methodology also revealed 2 advantages over solely measuring traditional sleep quality parameters by Nightcap (and, perhaps, also by polysomnography). First, the 3 newly developed Nightcap-based sleep quality parameters (EQI, RHYTHM, ELM/MIN NREM) proved to be more sensitive to treatment-related sleep disruption by these 2 agents than did Nightcap measurements of those traditional sleep quality variables used in polysomnographic studies. Second, in univariate ANOVAs, 2 of the 3 novel measures detected the significantly greater treatment-related sleep disruption by paroxetine versus fluvoxamine (shown also by MANOVA), whereas only 1 of 4 traditional measures revealed this difference.

The EQI and ELM/MIN NREM measures open a window on the physiology of sleep/arousal mechanisms. Neurons controlling the eyelid receive inputs from the reticular formation and also integrate the output of key structures involved in the sleep cycle control such as the locus ceruleus and the raphe nuclei. The eyelid sensor and its derived measures may therefore represent the most sensitive existing measure of vigilance level and of sleep quality parameters, directly reflecting the impulse traffic from the brain stem oculomotor centers, the reticular formation and its modulatory subdivisions.[29] Two related measures (EQI and ELM/MIN NREM) allow us to integrate, in 1 result, sleep physiology disruption as a loss of state demarcation with clinical/cognitive measures of disrupted sleep consolidation and increased vigilance.

Limitations of our approach mainly involve the lower physiologic resolution of the Nightcap compared with polysomnography. For example, the Nightcap cannot as yet differentiate the substages of NREM sleep and is also unable to provide data for spectral analyses. Such measures often reveal subtler drug effects on sleep. In addition, an increased sample size would greatly strengthen our results, since several study phase and drug effects appear only as statistical trends.

An important consideration for the interpretation of Nightcap-measured REM sleep variables in SSRI-treated individuals is the fact that drug-induced excessive eyelid movements can make the differentiation of light NREM sleep, REM sleep, and waking more difficult. We have addressed this problem in several ways. First, we have developed novel sleep quality measures such as EQI and RHYTHM that do not depend on the precise epoch-by-epoch stage differentiation of sleep. Second, scoring of REM and sleep onset latencies were done by hand (versus by algorithm), which allowed increased precision in identifying the first REM period as follows: (1) Hand scoring allowed identification of the first REM period to be based on the characteristic sinusoidal architecture of REM periods seen in untreated normals. (2) Hand scoring ensured that a period of eyelid quiescence (which likely corresponds to early-night NREM with its accompanying slow-wave sleep) intervened between the eyelid movements accompanying sleep onset and those attributable to REM onset.

Several studies[15,30,31] have shown the Nightcap to be able to accurately determine sleep latency compared with traditional polysomnography. Using standard multiple sleep latency test criteria for sleep onset (3 consecutive epochs of stage 1), the Nightcap detected sleep onset slightly sooner than polysomnography.[30] Since in that study[30] 2 consecutive minutes with less than 10 eyelid movements were required for the Nightcap to score sleep onset, it is clear that the Nightcap eyelid sensor is relatively insensitive to the slow eye movements of stage 1 NREM sleep. The currently used algorithm is conservatively designed to detect only macroarousals (awakening criteria: 1 minute with at least 200 eyelid movements, or at least 100 eyelid movements and 10 head movements or 3 consecutive minutes with at least 5 head movements; return-to-sleep criteria: 2 consecutive minutes with no more than 2 eyelid movements). Although the Nightcap shows some promise in detecting microarousals (unpublished observations 1997, 2001), the current algorithm does not detect these transient (though polysomnographically measurable) events.

While comparisons between polysomnography and Nightcap measures of the specific sleep quality parameters used in the current study are not reported here, their Nightcap-based values are computed from data that have been shown to agree closely between these 2 methods such as epoch-by-epoch sleep stage scoring[15,31] eyelid movements resulting from underlying eye movements,[32] and sleep onset latency measures.[15,30,31] Moreover, these values are obtained here using a simple, subject-applied, inexpensive, and noninvasive ambulatory monitor.

From a clinical point of view, our findings point to the high sleep-disruption price paid by depressed patients and raise further questions about the possible long-term effects on cognitive functions of these popular antidepressants.

Drug names: fluoxetine (Prozac), fluvoxamine (Luvox), ibuprofen (Motrin and others), paroxetine (Paxil).

REFERENCES

1. Hendrickse WA, Roffwarg HP, Grannemann BD, et al. The effects of fluoxetine on the polysomnogram of depressed outpatients: a pilot study. Neuropsychopharmacology 1994;10:85–91
2. Nicholson AN, Belyavin A, Pascoe PA. Modulation of rapid eye movement sleep in humans by drugs that modify monoaminergic and purinergic transmission. Neuropsychopharmacology 1989;2:131–143
3. Thase ME. Depression, sleep, and antidepressants. J Clin Psychiatry 1998;

59(suppl 4):55–65
4. Sharpley AL, Cowen PJ. Effect of pharmacologic treatments on the sleep of depressed patients. Biol Psychiatry 1995;37:85–98
5. Oberndorfer S, Saletu-Zyhlarz G, Saletu B. Effects of selective serotonin reuptake inhibitors on objective and subjective sleep quality. Pharmacopsychiatry 2000;42:69–81
6. Armitage R, Emslie G, Rintelmann J. The effect of fluoxetine on sleep EEG in childhood depression: a preliminary report. Neuropsychopharmacology 1997;17:241–245
7. Armitage R, Yonkers K, Cole D, et al. A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. J Clin Psychopharmacol 1997;17:161–168
8. Trivedi MH, Rush AJ, Armitage R, et al. Effects of fluoxetine on the polysomnogram in outpatients with major depression. Neuropsychopharmacology 1999;20:447–459
9. Armitage R, Trivedi M, Rush AJ. Fluoxetine and oculomotor activity during sleep in depressed patients. Neuropsychopharmacology 1995;12: 159–165
10. Schenck CH, Mahowald MW, Kim SW, et al. Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive-compulsive disorder. Sleep 1992;15:226–235
11. Winkelman J, Dorsey C, Cunnningham S, et al. Fluoxetine produces persistent rapid eye movements in non-REM sleep [abstract]. Sleep Res 1992;21:78
12. Dorsey CM, Lukas SE, Cunningham SL. Fluoxetine-induced sleep disturbance in depressed patients. Neuropsychopharmacology 1996;14: 437–442
13. Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol 1996;16:356–362
14. DeVane CL. Pharmacokinetics of the selective serotonin reuptake inhibitors. J Clin Psychiatry 1992;53(suppl 2):13–20
15. Ajilore O, Stickgold R, Rittenhouse CD, et al. Nightcap: laboratory and home-based evaluation of a portable sleep monitor. Psychophysiology 1995;32:92–98
16. Pace-Schott EF, Stickgold R, Matheson JK, et al. The Nightcap can distinguish patients with severe sleep disordered breathing (sdb) from patients with less severe sbd and controls [abstract]. Sleep Res 1995;24:488
17. Lipsey MW, Wilson DB. Practical Meta-Analysis. Thousand Oaks, Calif: Sage Publications; 2000
18. Howell DC. Statistical Methods for Psychology. 4th ed. Belmont, Calif: Duxbury Press; 1997
19. Cohen J. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Hillsdale, NJ: Erlbaum; 1988
20. Richelson E. The pharmacology of antidepressants at the synapse: focus on newer compounds. J Clin Psychiatry 1994;55(9, suppl A):34–41
21. Tulloch IF, Johnson AM. The pharmacologic profile of paroxetine: a new selective serotonin reuptake inhibitor. J Clin Psychiatry 1992;53 (2, suppl):7–21
22. Vogel GW, Buffenstein A, Minter K, et al. Drug effects on REM sleep and on endogenous depression. Neurosci Biobehav Rev 1990;14:49–63
23. Gaillard JM, Nicholson AN, Pascoe PA. Neurotransmitter systems. In: Kryger M, Roth T, Dement W, eds. Principles and Practice of Sleep Medicine. 2nd ed. Philadelphia, Pa: WB Saunders; 1994:338–348
24. Hobson JA, Stickgold R, Pace-Schott EF. The neuropsychology of REM sleep dreaming. Neuroreport 1998;9:R1–R14
25. Steriade M, McCarley RW. Brainstem Control of Wakefulness and Sleep. New York, NY: Plenum; 1990
26. Kupfer DJ, Perel JM, Pollock BG, et al. Fluvoxamine versus desipramine: polysomnographic effects. Biol Psychiatry 1991;29:23–40
27. Armitage R. Effects of antidepressant treatment on sleep EEG in depression. J Psychopharmacol 1996;10(suppl 10):22–25
28. Saletu B, Frey R, Krupka M, et al. Sleep laboratory studies on the single-dose effects of serotonin reuptake inhibitors paroxetine and fluoxetine on human sleep and awakening qualities. Sleep 1991;14:439–447
29. Goldberg ME, Eggers HM, Gouras P. The oculomotor system. In: Kandel EF, Schwartz HH, Jessell TM, eds. Principles of Neural Science. Norwalk, Conn: Appleton & Lange; 1991:660–678
30. Stickgold R, Pace-Schott EF, Hobson J, et al. Comparison of Nightcap and polysomnography in detection of sleep onset using a modified MSLT protocol [abstract]. Sleep Res 1997;26:693
31. Yun B, Obermeyer WH, Benca RM. Nightcap assessment of home and laboratory sleep [abstract]. Sleep Res 1997;26:238
32. Stickgold RA, Xie Z, Hobson JA. Quantification of rapid eye movements with the Nightcap [abstract]. Sleep Res 1996;25:534