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Prominent Eye Movements During NREM Sleep and REM Sleep Behavior Disorder Associated with Fluoxetine Treatment of Depression and Obsessive–Compulsive Disorder

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Summary: The clinical polysomnographic (PSG) reports of 2,650 consecutive adults studied during 41 months were reviewed retrospectively to identify all patients treated with fluoxetine or tricyclic antidepressants. The PSG reports of four other adult groups were also reviewed: periodic limb movement (PLM) disorder (n = 28); sleep terror/sleepwalking (ST/SW) (n = 54); rapid eye movement (REM) sleep behavior disorder (RBD) (n = 70); patients with clinically unremarkable sleep during two consecutive PSG studies (n = 30). Standard PSG recording and scoring methods were employed. A total of 1.5% (n = 41) and 2.0% (n = 52) of patients were receiving fluoxetine or tricyclics (amitriptyline or nortriptyline, n = 31; imipramine or desipramine, n = 16; protriptyline or trimipramine, n = 5). A selective association between fluoxetine and extensive, prominent eye movements in nonrapid eye movement (NREM) sleep was detected, utilizing Fisher's exact one-tailed statistic ($p < 0.00001$ for each comparison). The detection rates were fluoxetine, 48.8% (20/41); tricyclics, 5.8% (3/52); RBD, 4.3% (3/70); objectively normal sleepers, 3.3% (1/30); PLM, ST/SW, 0% (0/82). These groups had similar mean ages (31.5–45.4 years) and gender distributions (50.0–60.7% male), apart from RBD. The effect of fluoxetine, a potent and specific serotonin reuptake inhibitor, on NREM eye movements is postulated to derive from potentiation of serotonergic neurons that inhibit brainstem "omnipause neurons", which, in turn, inhibit saccadic eye movements, thus resulting in disinhibited release of saccades. In addition, a 31-year-old man with obsessive–compulsive disorder developed RBD soon after starting fluoxetine therapy, which persisted at PSG study 19 months after fluoxetine discontinuation. **Key Words:** Fluoxetine—NREM sleep eye movements—Polysomnography—Obsessive–compulsive disorder—Serotonin—REM sleep behavior disorder—Depression.

Fluoxetine, the most widely prescribed antidepressant (1), is a potent serotonin synaptic reuptake inhibitor that has been reported to display a unique polysomnographic (PSG) feature consisting of prominent eye movements in nonrapid eye movement (NREM) sleep (2). PSG data on fluoxetine in humans are scarce, with four reports on acute dosing effects (3–6) and two reports on chronic effects in depressed patients (2,7).

We now report data from all clinical PSG studies of patients receiving fluoxetine treatment during a 41-month interval at our center, addressing the issue of eye movement abnormalities during NREM sleep and reviewing our cumulative experience with this bicyclic antidepressant. A case of fluoxetine-induced rapid eye movement (REM) sleep behavior disorder (RBD) (8,9) will also be presented.

METHODS

A research assistant reviewed the hospital chart reports of every clinical PSG study performed on 2,650 consecutive adult patients (≥18 years of age) at our center from January 1988 (when fluoxetine was first marketed in the United States) through May 1991 in order to identify all patients being treated with fluoxetine or with tricyclic antidepressants at the time of their PSG studies. The following data were extracted

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from the charts: medications and dosages, clinical diagnoses before and after the PSG studies, sleep architecture measures and specific descriptive comments about eye movements during NREM sleep.

The PSG reports of four other adult comparison groups from our center were also reviewed: 1) periodic limb movement (PLM) disorder (8) in 28 consecutive patients clinically evaluated and treated by one of the authors; 2) sleep terrors/sleepwalking (ST/SW) (8) in 54 consecutive patients identified in a series of 100 patients with sleep-related injury (10); 3) RBD in a series of 70 consecutive patients (9); 4) clinically unremarkable PSG studies on two consecutive nights in 30 consecutive patients: "objectively normal sleepers".

All PSG studies utilized standard recording and scoring procedures (11), in which there was monitoring of the electrooculogram (EOG), electroencephalogram (EEG), electrocardiogram (EKG), airflow by nasal–oral thermocouples and submental/bilateral anterior tibialis electromyograms (EMGs). There was continuous audiovisual monitoring during each PSG study. Expanded EEG, EMG and respiratory monitoring was employed in the evaluation of suspected nocturnal seizures, parasomnia or obstructive sleep apnea (OSA), as previously described (10).

RESULTS

Of the 2,650 consecutive adult patients undergoing PSG studies, 1.5% (n = 41, including one patient originally identified in 1983) had been receiving treatment with fluoxetine [for major depression/dysthymia (n = 40) or for obsessive–compulsive disorder (OCD, n = 1)], and 2.0% (n = 52) had been receiving treatment with tricyclic antidepressants [for various depressive disorders and/or insomnia: amitriptyline (n = 23), nortriptyline (n = 8), imipramine (n = 10), desipramine (n = 6), protriptyline (n = 4), trimipramine (n = 1)]. All patients had been receiving fluoxetine or tricyclic treatments chronically for months or years. The information contained in the charts was insufficient to allow a direct comparison of the psychiatric status in patients treated with fluoxetine or tricyclics.

NREM sleep eye movement abnormalities

A selective and highly significant association between fluoxetine treatment and extensive, prominent eye movements in NREM sleep was detected, when analyzing the fluoxetine group with the five comparison groups, utilizing Fisher's exact one-tailed statistic ($p < 0.00001$ for each comparison). The detection rates for abnormal NREM eye movements were as follows: fluoxetine, 48.8% (20/41); tricyclics, 5.8% (3/52); RBD, 4.3% (3/70); objectively normal sleepers, 3.3% (1/30); ST/SW, 0% (0/54); PLM disorder, 0% (0/28).

These groups had comparable mean ages and gender frequencies, apart from RBD: fluoxetine, 39.1 ± (SD) 8.6 years (51.2% male); tricyclics, 45.4 ± 14.6 years (50.0% male/female); PLM disorder, 41.0 ± 15.3 years (60.7% male); ST/SW, 31.5 ± 9.9 years (61.1% male); RBD, 59.3 ± 15.4 years (90.0% male); objectively normal sleepers, 37.3 ± 13.9 years (60.0% male).

Figure 1 illustrates the typical fluoxetine-associated EOG findings during stage 2 NREM sleep, with frequent and prolonged runs of high-voltage rapid and slow eye movements. These abnormalities are present throughout most of stages 1 and 2 sleep and usually attenuate or disappear during stage 3/4 sleep, although five patients displayed persistent eye movements throughout stage 3/4 sleep.

The fluoxetine and tricyclic groups each contained a subgroup of patients with OSA who were treated with nasal continuous positive airway pressure (CPAP) during the second half of their PSG studies, resulting in major alterations of sleep continuity and architecture, and the detection rate for abnormal NREM eye movements was distinctly lower in these subgroups: fluoxetine, 18.7% (3/16); tricyclics, 4.8% (1/21) (NS, Fisher's exact one-tailed test).

Given a wide range of tricyclic dosages, the subgroup of patients without OSA receiving intermediate to high doses of tricyclics (n = 17) was then compared with the fluoxetine subgroup without OSA (n = 25), and significant differences were evident, as seen in Table 1. Combined treatment of either fluoxetine or of tricyclics with other psychotropic agents, particularly benzodiazepines, produced no apparent differences in detected NREM eye movement abnormalities compared to their respective monotherapies.

For the fluoxetine group (I) in Table 1, the detection rates for NREM eye movement abnormalities were 50.0% (5/10) before and 80.0% (12/15) after the original abstract calling attention to this phenomenon was published in June 1990 (2). Three polysomnographers interpreted the PSG studies of the 25 fluoxetine patients listed in Table 1, and their individual rates of reporting NREM eye movement abnormalities were 100% (5/5), 71.4% (10/14) and 42.9% (3/7) (two polysomnographers independently detected the abnormalities during separate PSG studies of the same patient). Thus, all three polysomnographers had distinctly higher rates of detecting sleep ocular disturbances with fluoxetine treatment compared to tricyclic treatment.

Data for the seven patients (four female) not treated with fluoxetine who were found to have excessive NREM eye movements are as follows: two females, aged 29 and 55 years, exhibited profoundly disturbed sleep architecture while receiving amitriptyline 25 mg

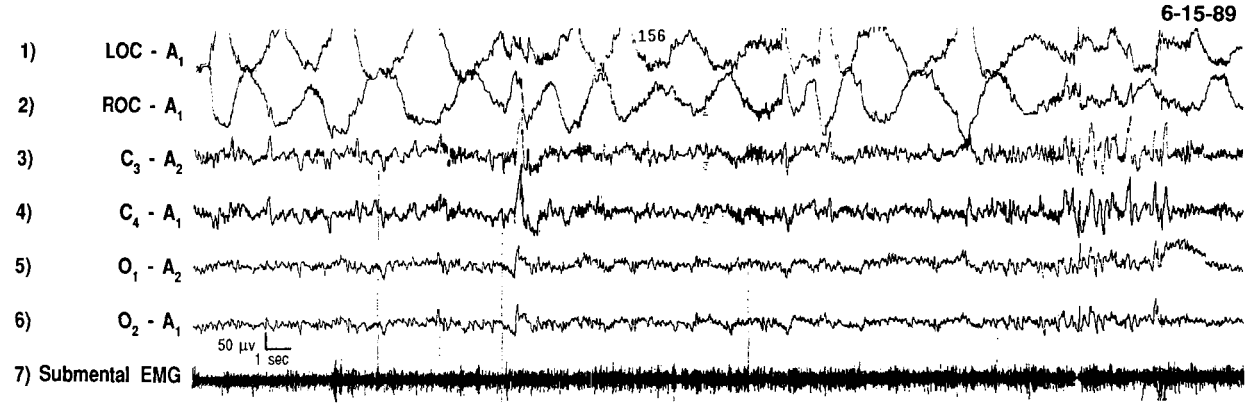

FIG. 1. Polysomnogram of fluoxetine-related prominent eye movements during NREM sleep. High-voltage, rapid and slow eye movements (1 and 2) are present continuously throughout this 42-second tracing. Sleep spindles and K-complexes (3 and 4) indicate stage 2 NREM sleep. Similar eye movements are present during most of stages 1 and 2 sleep during the entire sleep cycle.

at bedtime or imipramine 150 mg at bedtime; a 36-year-old female with OSA and CPAP treatment while receiving amitriptyline 200 mg hs and trazodone 300 mg hs had discontinued fluoxetine 1 year previously after a 3-month course of 20 mg/day; a 40-year-old male with RBD had a remote history of severe amphetamine/ethanol abuse, currently in longstanding remission; two elderly males with RBD had brainstem neurodegenerative disorders; a 28-year-old female with objectively normal sleep denied any history of psychotropic drug use.

A 32-year-old female patient was originally found to have profoundly abnormal NREM eye movements in 1983, during PSG studies evaluating the complaint of daytime somnolence, while she was receiving fluoxetine treatment of depression during premarketing clinical trials. However, she was abusing diazepam at the time, with serum diazepam/desmethyldiazepam levels of 1,415 ng/ml. Serial PSG studies during the subsequent 1–3 years, with negative urine toxicology screens and reported drug abstinence, revealed the per-

TABLE 1. *Electrooculographic (EOG) abnormalities during NREM sleep*[a]

Clinical groups	% (+) EOG abnormalities	Age, mean (±SD)	% Female (n)	% Male (n)	Comments
Fluoxetine (I)					
1) Monotherapy	72.7 (8/11)	35.5 (6.9)	54.5 (6)	45.5 (5)	Mean daily dose: 38.2 mg, range 20–80
2) Combination therapy[b]	64.3 (9/14)	37.9 (9.6)	85.7 (12)	14.3 (2)	Mean daily dose: 34.2 mg, range 20–80
3) Total groups 1 and 2	68.0 (17/25)	36.8 (8.1)	72.0 (18)	28.0 (7)	Mean daily dose: 36.0 mg, range 20–80
Tricyclic antidepressants (II)					
1) Amitriptyline (≥100 mg/day), or nortriptyline (≥50 mg/day)	0.0 (0/11)	39.1 (17.1)	54.5 (6)	45.5 (5)	Mean daily doses: amitriptyline (n = 6), 166.7 mg, range 100–300 mg; nortriptyline (n = 5), 80.0 mg, range 50–125 mg
2) Imipramine (≥100 mg/day), or desipramine (≥100 mg/day)	16.7 (1/6)	47.2 (13.8)	66.7 (4)	33.3 (2)	Mean daily doses: imipramine (n = 5), 170.0 mg, range 100–300 mg; desipramine (n = 1), 150 mg
3) Total, groups 1 and 2[c]	5.9 (1/17)	41.9 (16.1)	58.8 (10)	41.2 (7)	

[a] Statistics: Fisher's exact one-tailed tests revealed significant differences between fluoxetine (Group I) and tricyclics (Group II): Group I (3) vs. Group II (3), p = 0.00005; Group I (3) vs. Group II (1), p = 0.0001; Group I (3) vs. Group II (2), p = 0.03.

[b] Benzodiazepines, n = 10 (clonazepam, 2–4 mg/day, n = 5; triazolam, 0.125 mg hs; chlorazepate, 7.5 mg hs; alprazolam, 0.5 mg/day; temazepam, 60 mg hs; diazepam, toxic doses); anticonvulsants, n = 4 (carbamazepine, 800 and 1,000 mg/day, n = 2; phenobarbital, 180 mg/day; mysoline 500 mg/day); others, n = 4 (trazodone, 200 mg hs; lithium carbonate, 900 mg/day; perphenazine, 4 mg/day; trifluoperazine, 2 mg/day).

[c] Four of the 17 patients were on combination therapy: benzodiazepines, n = 3 (clonazepam, 0.5 and 3.0 mg/day; alprazolam, 1.5 mg/day); others, n = 5 (loxapine, 125 mg/day; chlorpromazine, 75 mg/day; benztropine, 4 mg/day; lithium carbonate, 900 mg/day; methylphenidate, 30 mg/day).

sistence of prominent NREM eye movements, with an eventual incomplete attenuation.

Clinical findings

The sleep architecture measures for the fluoxetine monotherapy group are contained in Table 2. The sleep efficiency and stage 3/4% have moderate reductions, stage 1% and sleep latency have mild elevations, REM% is not suppressed and REM latency is considerably prolonged. Apart from a shift toward lighter sleep, the sleep architecture and the customary NREM–REM cycling are preserved.

The final primary clinical diagnoses after the PSG studies for the fluoxetine and tricyclic groups were as follows: OSA [39.0% (16/41) vs. 40.4% (21/52)], PLM disorder [36.6% (15/41) vs. 25.0% (13/52)], no objective clinical findings [19.5% (8/41) vs. 28.8% (15/52)], RBD [2.4% (1/41) vs. 1.9% (1/52)] and narcolepsy [2.4% (1/41) vs. 3.8% (2/52)]. Fluoxetine appeared to have induced RBD in one case, to be described below, but, in contrast, a tricyclic (desipramine, 30 mg/day) was not causally related to the other case of RBD, which had emerged prior to its use. No patient had presented with a complaint of fluoxetine or tricyclic-induced insomnia.

Subclinical RBD (12) (characterized by prominently increased submental EMG tone and/or enhanced phasic EMG activity during REM sleep, but without clinical correlates and with uncertain prognostic significance) was detected in 14.6% (6/41) of fluoxetine patients (six women, mean age 36.7 ± 8.2 years), and in 3.8% (2/52) of tricyclic patients (a 32-year-old woman and a 37-year-old man receiving imipramine 150 mg at bedtime or 100 mg/day).

The following case, which satisfies DSM-III-R criteria for OCD (13), documents another class of medication that can induce RBD.

TABLE 2. *Sleep architecture measures in chronic fluoxetine monotherapy*[a]

Measures	Mean (± SD)
Total sleep time, minutes	456.4 (118.0)
Sleep efficiency, % (minutes asleep/minutes in bed)	82.2 (13.4)
Awakenings, number (arousals >30 seconds)	9.3 (4.0)
Stage 1%	11.3 (8.4)
Stage 2%	56.9 (8.7)
Stage 3/4%	9.4 (7.2)
REM%	22.4 (7.2)
REM latency, minutes	147.9 (68.7)
Sleep latency, minutes[b]	45.8 (65.2)

[a] n = 11; mean age 35.5 (±6.9) years; 54.5% (6/11) female. Data from first-night polysomnographic studies. Mean fluoxetine dose, 38.2 mg/day (range: 20–80 mg).
[b] Latency to 5 continuous minutes of sleep (regardless of stage).

CASE REPORT

Clinical history

A 31-year-old man had a 20-year history of OCD, with obsessive fears of contamination, daily washing rituals and compulsive "checking things over and over again". He had slept in the same bed as his wife for 13 years, and she had not observed any disturbance in his sleep. He worked as a draftsman out of his home, but became productive only after being treated with fluoxetine, 20 mg twice daily, which promptly relieved OCD symptoms, as reflected by psychometric scores at 3 months follow-up compared to immediately before treatment: Leyton Obsessional Inventory (LOI) (14) [total symptom and trait score (8 vs. 60), resistance score (3 vs. 60), interference score (0 vs. 70)]; Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) (15,16) (0 vs. 25); Hamilton Depression Scale (HAM-D, 17 item) (5 vs. 18); and Symptom Checklist-90 (SCL-90) [global severity (0.2 vs. 2.4), obsessive–compulsive (0.2 vs. 3.2), depression (0.15 vs. 2.6), anxiety (0.4 vs. 2.8)].

Shortly after starting fluoxetine treatment, the patient developed a sleep disorder in which he would attempt to enact altered dreams of being threatened or attacked and when he retaliated in the dreams he would actually be striking his wife in bed or else colliding with furniture. His wife observed prominent limb jerking almost nightly and also punching, kicking and shouting twice weekly. His action-filled dreams did not include any waking OCD behaviors or obsessions. After 11 months of treatment with fluoxetine, the patient informed his psychiatrist (S.W.K.) about his sleep disorder and was referred for clinical sleep–wake evaluation.

PSG data

Table 3 contains the longitudinal PSG data. A urine toxicology screen was negative for any illicit substance during all five first-night PSG studies. The fluoxetine/norfluoxetine serum levels during PSG study 1 were within the midtherapeutic range for our laboratory (300–1,150 ng/ml); detectable serum levels 2 months after fluoxetine discontinuation should be noted. The approximate half-lives of fluoxetine and norfluoxetine in this patient were 15 and 20 days, respectively.

During active fluoxetine treatment (PSG studies 1 and 2) compared to after fluoxetine discontinuation, the sleep latency and REM latency were prolonged, sleep disruption (awakenings, total arousals, hourly arousals) was greater, stage 1 sleep% was higher and

TABLE 3. *Polysomnographic (PSG) data in a 31-year-old man with obsessive–compulsive disorder and fluoxetine-induced REM sleep behavior disorder*

Dates of PSG studies (month-day-year)	Medication status	Sleep onset and continuity[a]							Sleep architecture[b]				
		Sleep latency (minutes)[c]	REM latency (minutes)[d]	Total sleep time (minutes)	Sleep efficiency (%)[e]	Awakenings (number)[f]	Arousals (total number)[g]	Arousals (number/hour)	Stage 1%	Stage 2%	Stage 3/4%	REM %	REM density (± SD)[h]
1) 6-14-89	Fluoxetine 40 mg/	77	194	421	68.4	34	373	53	19.8	42.0	12.3	25.9	3.4 (1.8)
2) 6-15-89	day, (14.5 month regimen)[i]	52	106	591	85.7	21	496	50	10.3	52.8	5.3	31.6	3.7 (1.9)
3) 11-20-89	2 months after	39	87	515	86.5	18	261	30	10.2	44.8	11.7	33.3	2.4 (1.4)
4) 11-21-89	fluoxetine discontinuation[j]	41	68	582	93.4	6	177	18	6.9	38.5	17.5	37.1	3.3 (1.8)
5) 2-26-90	5 months after fluoxetine discontinuation[k]	36	61	572	84.7	11	198	21	14.0	48.3	10.1	27.6	2.9 (1.8)
6) 7-09-90	9.5 months after	33	63	482	87.5	10	241	30	4.4	52.3	14.7	28.6	2.8 (1.7)
7) 7-10-90	fluoxetine discontinuation[l]	37	45	435	84.5	9	183	25	10.5	42.5	17.5	29.5	2.8 (1.6)
8) 5-09-91	19 months after fluoxetine discontinuation	38	59	422	74.1	13	167	24	14.2	51.2	10.3	24.3	2.1 (2.0)

[a] Results rounded off to the nearest integer for sleep latency, REM latency, total sleep time and arousals (number/hour).
[b] Comprises the percentage of total sleep time for each sleep stage.
[c] Latency to 5 continuous minutes of sleep.
[d] Latency to REM sleep, less intervening wakefulness.
[e] Time asleep (minutes)/time in bed (minutes).
[f] Arousals >30 seconds in duration.
[g] Frequently associated with periodic or aperiodic EMG twitching.
[h] REM density (RD) = RA/RT, with REM activity (RA) scored on a 0–8 scale during successive 1-minute intervals of REM (sleep) time (RT).
[i] Serum level: fluoxetine, 369 ng/ml + norfluoxetine, 231 ng/ml = 600 ng/ml.
[j] Serum level: fluoxetine, 20 ng/ml + norfluoxetine, 30 ng/ml = 50 ng/ml.
[k] Serum level: fluoxetine, <5 ng/ml + norfluoxetine, <5 ng/ml = <10 ng/ml.
[l] During PSG studies 6 and 7 the patient was receiving propranolol, 80 mg/day for hypertension.

REM density was higher [as determined by an established method (17)].

The REM% was elevated (>25%) during seven of the eight PSG studies, with propranolol perhaps contributing to this finding in two of the PSG studies. REM latency was notably reduced during the final five PSG studies.

RBD was diagnosed during all eight PSG studies, including the three PSG studies completed 9.5 months and 19.0 months after fluoxetine discontinuation. The most prominent behaviors occurred during PSG studies 2, 3 and 5, and were typical for RBD. There was generalized limb and trunk jerking, and he would punch the bed, kick, shake his head vigorously and shout. Sexual or feeding behaviors were never observed.

Most of the arousals and awakenings listed in Table 1 were associated with periodic or aperiodic movements of NREM sleep. During PSG 5, an extraordinary number of NREM movements were recorded (n = 1,081), with a mean of 113/hour. However, because the arousal rate for PSG 5 was only 21/hour, most of these movements were not associated with arousals.

Figures 2–4 depict common PSG findings in this patient. In all eight PSG studies, submental EMG atonia was maintained for >50% of each REM sleep period, despite intense phasic EMG activity of the limbs, as illustrated by these figures. High-voltage rapid and slow eye movements during NREM sleep were present during all eight PSG studies.

Clinical evaluations and outcome

The patient discontinued fluoxetine during 9/89, with partial relapse of OCD emerging 4 months later. However, RBD by history and by PSG studies did not remit during this same period. A neurologic consultation (with M.W.M.), prompted by the identification of RBD, revealed a history of isolated, generalized tonic–clonic seizure at age 4 years, with anticonvulsant therapy being maintained for 9 years. A closed head injury at age 14 years resulted in a brief loss of consciousness. Lifelong stuttering had resolved spontaneously at age 26 years, with brief, stress-induced recurrences. Examination revealed a resting pulse of >100/minute; diaphoresis; generalized, prominent tremulousness resembling choreoathetotic movements; diffuse, mild

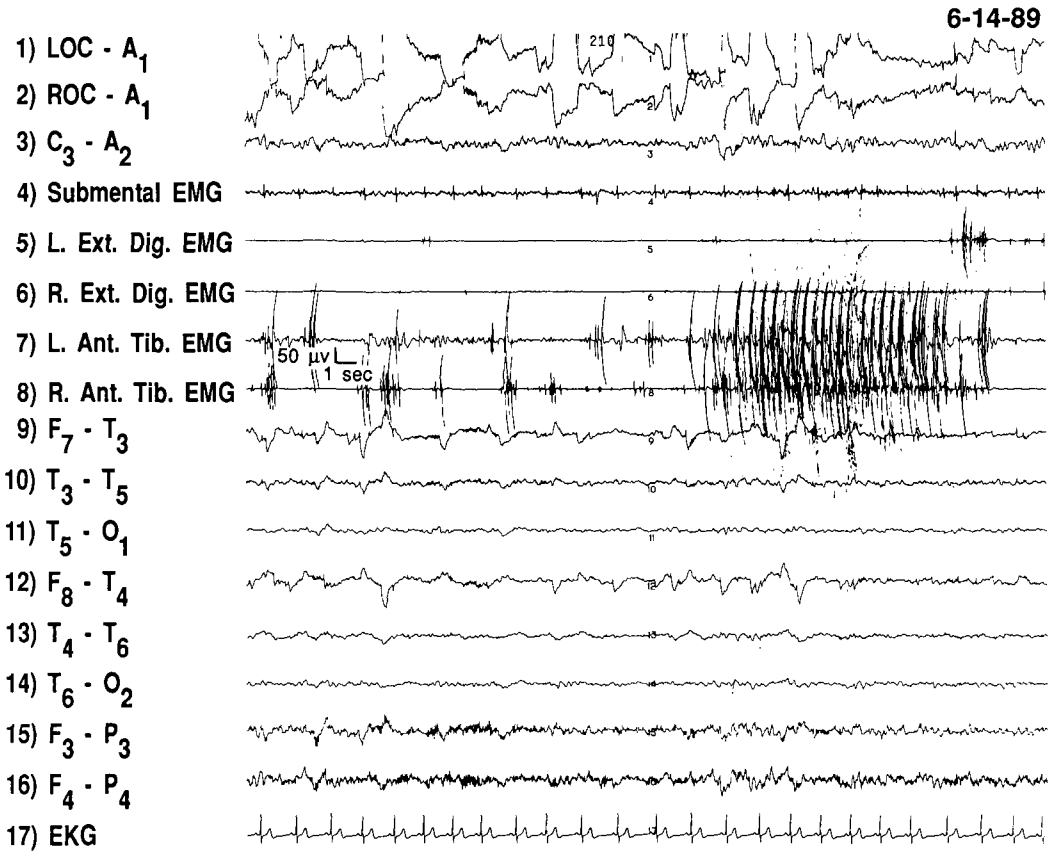

FIG. 2. Polysomnogram documenting REM sleep motor dyscontrol in a fluoxetine-treated patient. Sustained bursts of intense EMG twitching emerge almost exclusively in the legs (7 and 8), accompanied by dense REM activity (1 and 2), with maintenance of background atonia (4). The EEG is consistently activated throughout the tracing (3 and 9–16), and the EKG (17) remains constant without acceleration, indicating an ongoing REM state rather than arousal.

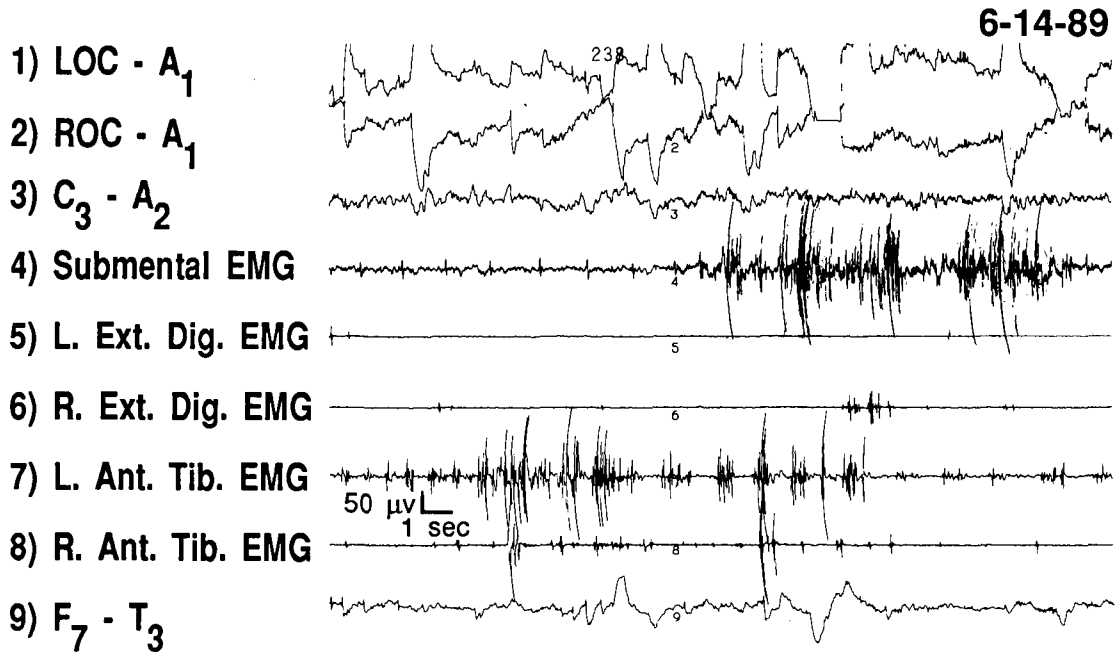

FIG. 3. REM sleep polysomnogram 9 minutes after Fig. 2. REM activity remains dense (1 and 2). The left leg EMG (7) at first is preferentially activated during complete submental EMG atonia (4). However, a major reversal then occurs after a 6-second transition period, resulting in sustained submental EMG twitching and nearly complete suppression of left leg EMG twitching.

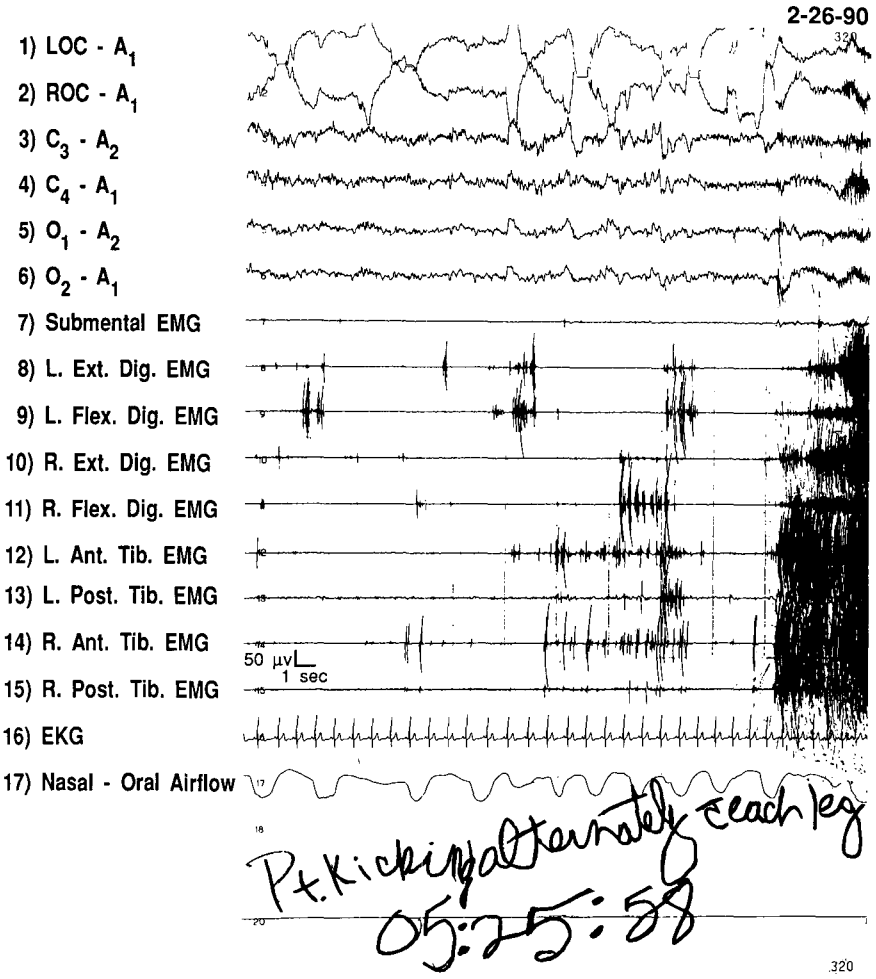

FIG. 4. Polysomnogram of kicking during REM sleep. A technician notes kicking of both legs, and six of the eight limb EMGs (8–15) show excessive twitching despite full maintenance of background atonia (7). REM activity is prominent (1 and 2). The lack of tachycardia (16) during repetitive kicking should be noted [EEG: (3–6)].

muscle weakness and symmetrically brisk reflexes without clonus. Akathisia was not evident by history or examination, nor was there indication of extrapyramidal dysfunction. The only medication the patient was receiving at the time of examination was propranolol. A magnetic resonance imaging brain scan was normal.

An endocrinologic consultation was obtained. Thyroid functions, determined by radioimmune assay, indicated a euthyroid status, with a T4 level of 9.5. The blood pressure was 154/110, a full blood chemistry panel was normal, and the serum CK and aldolase levels were not elevated. Replacement of propranolol (a β-adrenergic antagonist) with nifedipine (a calcium channel antagonist) 30 mg/day, promptly remitted the hypertension, reduced the tremulousness and diaphoresis but had no impact on the OCD or RBD. At follow-up 27 months after fluoxetine was discontinued, the patient reported only slight diminution of RBD, but there was substantial remission of OCD and complete remission of depression while he was receiving nifedipine as his only medication. Treatment with clonazepam had been offered, on account of its established efficacy in RBD (9) and its anecdotal efficacy in OCD (18,19), but the patient demurred.

DISCUSSION

NREM sleep eye movement abnormalities

This report corroborates the findings from a previous abstract (2) indicating that fluoxetine has a strong propensity for inducing extensive, prominent eye movement activity during NREM sleep. The original description of this phenomenon involved seven females (mean age, 24.0 ± 7.9 years) who complained of fluoxetine-induced insomnia while receiving 50.0 ± 25.0 mg/day as treatment for major depression or bu-

limia nervosa (2). Our report has also identified this abnormality in males, in the fluoxetine treatment of dysthymia or OCD, and in patients without complaints of fluoxetine-induced insomnia. However, the retrospective data cannot indicate whether there are serum level, time course, age-related or psychopathology-related thresholds for the emergence of these atypical NREM eye movements.

The previous documentation in one patient of NREM eye movement abnormalities being present during—but not immediately before—fluoxetine treatment (2) implicated fluoxetine as a causal influence. The persistence of NREM ocular abnormalities, with only mild attenuation, for as long as 19 months after fluoxetine discontinuation in our patient with RBD suggests that fluoxetine can exert long-lasting effects upon the central nervous system. This possibility may be relevant to the one patient in our series receiving low-dose amitriptyline together with trazodone while displaying NREM eye movements, who had discontinued fluoxetine 1 year previously.

The initial report on EOG findings during fluoxetine treatment quantitated the pervasive presence of intrusive eye movements for each 1-minute interval during NREM sleep (2): stage 1, 89.0 ± 7.9% of epochs, with a mean 5.0 ± 3.0 eye movements/minute; stage 2, 73.4 ± 14.0% of epochs, with a mean 3.4 ± 2.2 eye movements/minute; stage 3/4 had a lower frequency.

A comprehensive textbook on sleep medicine states, in part, the following with regard to eye movement activity during NREM sleep (20) (brackets within the quotes are our insertion): "The onset of sleep in most humans is accompanied by slow, rolling eye movements which also occur with transitions to stage 1 during the night . . . At the beginning of the night, slow eye movements may infrequently and only very briefly persist after the appearance of sleep spindles and K complexes . . . [i.e. onset of stage 2 sleep]. Eye movements do not occur during stages 3 and 4 sleep".

Clomipramine, another potent serotonin synaptic reuptake inhibitor, has been documented, in a 52-year-old depressed male, to induce "extreme changes in the electrooculogram . . . slow and rapid eye movements occurred throughout the nightime recordings in all stages of sleep" (21).

Although our data suggest that fluoxetine has a special propensity for inducing prominent oculomotor activity during NREM sleep, which is not shared by frequently prescribed tricyclic antidepressants (nor shared by clinical sleep disorders involving motor dyscontrol), only prospective studies involving a broad range of psychotropic medications will provide a definitive statement on the specificity of this fluoxetine effect. Such studies would benefit from direct current (dc), automated quantitative recording of the EOG to determine the frequency and patterns of horizontal and vertical eye movements, the presence of square-wave jerks (i.e. saccades), etc. These data could be compared with the recently identified eye movement patterns in REM sleep (22), which is relevant because the EOG activity during NREM sleep in our fluoxetine-treated patients covered the spectrum of typical stage 1 slow, rolling eye movements to the typical REMs of REM sleep. The EOG effects of fluoxetine, in prospective studies, may also be compared with those of other serotonin reuptake inhibitors.

A state of serotonin hyperstimulation known as the "serotonin syndrome" (23) has been described with various medications—most commonly combinations of L-tryptophan, monoamine oxidase inhibitors and fluoxetine—and can involve myoclonic jerks, "ocular oscillations" (24,25) and various other motor and autonomic signs during wakefulness. The mechanisms responsible for the excessive saccadic eye movements (i.e. square-wave jerks) of the serotonin syndrome have been postulated to involve overactive serotonergic neurons in the brain stem, which inhibit omnipause neurons in the brain stem, thus releasing (through disinhibition) the saccadic movements that ordinarily are suppressed by the omnipause neurons (24). A very similar condition involving "irrepressible saccadic eye movements" has been documented with a state of catecholamine (dopamine and norepinephrine) depletion induced by metyrosine (26), leading to the comment that "triggering of saccades entails interaction of many neuronal circuits, and several other transmitter substances may play important roles in modulating this triggering" (26).

PSG studies have not been reported in conjunction with the serotonin syndrome, nor with other saccadic release states. It is therefore possible that our findings of EOG abnormalities in NREM sleep may constitute a mild form of serotonin syndrome in sleep induced by fluoxetine. Neuroophthalmic testing of fluoxetine-treated patients will determine whether they also show intrusive saccades during wakefulness. In addition, PSG studies of patients with the serotonin syndrome will detect the presence or absence of associated NREM ocular abnormalities. Serial PSG and neuroophthalmic studies of patients who had previously overdosed on fluoxetine (27) may provide useful data concerning the long-term effects on oculomotor functioning in sleep and waking.

RBD

Our data justify the preliminary conclusion that fluoxetine is similar to the tricyclic antidepressants in its capacity to induce clinical or subclinical RBD (28,29,

and as reviewed in 30). In the case of fluoxetine-induced RBD, the history provided by the patient's wife virtually excludes any preexisting parasomnia. The dream disturbance was very typical for RBD and did not incorporate any of the patient's OCD activity. Similarly, in two cases of chronic RBD triggered by severe adjustment disorders (10,31), dream disturbance was restricted to typical RBD dreams, without any posttraumatic dreams.

The pathophysiology of RBD in humans is obscure insofar as most cases emerge either idiopathically or with diverse neurologic disorders (9). OCD in our patient may have been a predisposing factor for RBD on the basis of subtle brain structural changes, given recent data from positron emission tomography brain scan studies showing that OCD patients have dysfunction in the orbital prefrontal cortex and the striatum (32) and also given recent findings of increased amounts neurologic "soft signs" in medication-free OCD patients (33).

Concerning sleep in OCD, one PSG report on 14 patients found a shortened REM latency, and there was no mention of motor dysfunction (34).

The pharmacologic profile of fluoxetine does not readily suggest a pathophysiologic mechanism for inducing RBD. Fluoxetine is a highly specific serotonin synaptic uptake inhibitor, without affinity for a wide variety of neuronal receptors (35,36), which has reported efficacy in treating OCD (37–41). With regard to the neurochemistry of REM sleep, the onset of REM sleep is mediated by cholinergic mechanisms, the REM-atonia is mediated by glycine or a glycinergic substance, and the phasic motor excitation is mediated by a non-*N*-methyl-D-aspartate excitatory neurotransmitter (42). Therefore, the manner in which this REM sleep neurochemical system can be perturbed by a serotonergic reuptake blocker such as fluoxetine awaits identification.

Fluoxetine has been reported to induce various forms of reversible extrapyramidal dysfunction in wakefulness, including acute dystonia, akathisia, bradykinesia, rigidity and tremor (43–49). Fluoxetine has also been implicated in the development of tardive dyskinesia (50,51), a condition that often is irreversible. Furthermore, a study in rats has identified fluoxetine-induced inhibitory effects on extrapyramidal dopamine neurons (52).

The prospect that fluoxetine may induce prominent and long-standing alterations in central nervous system functioning, as reflected by NREM eye movements, RBD and extrapyramidal dysfunction, should be of interest to clinicians and basic scientists. Polysomnographers should be alerted to the NREM oculomotor effects of fluoxetine, and physicians prescribing fluoxetine should be aware that fluoxetine shares with the tricyclic antidepressants in the capacity to induce clinical or subclinical RBD.

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