SSRI Treatment suppresses dream recall frequency but increases subjective dream intensity in normal subjects

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SUMMARY   Clinical lore and a small number of published studies report that the selective serotonin reuptake inhibitors (SSRIs) intensify dreaming. This study examines the dream effects of paroxetine and fluvoxamine in order to both increase clinical knowledge of these agents and to test an important potential method for probing the relationship between REM sleep neurobiology and dreaming in humans. Fourteen normal, paid volunteers (4 males, 10 females; mean age 27.4 year, range 22–39) free of medical or neuropsychiatric symptoms as well as of psychotropic or sleep affecting drugs completed a 31-day home-based study consisting of: 7 days drug-free baseline; 19 days on either 100 mg fluvoxamine (7 Ss) or 20 mg paroxetine (7 Ss) in divided morning and evening doses; and 5 days acute discontinuation. Upon awakening, subjects wrote dream reports, self-scored specific emotions in their reports and rated seven general dream characteristics using 5-point Likert scales. Dream reports were independently scored for bizarreness, movement and number of visual nouns by three judges. REM sleep-related measures were obtained using the Nightcap ambulatory sleep monitor. Mean dream recall frequency decreased during treatment compared with baseline. Dream report length and judge-rated bizarreness were greater during acute discontinuation compared with both baseline and treatment and this effect was a result of the fluvoxamine-treated subjects. The subjective intensity of dreaming increased during both treatment and acute discontinuation compared with baseline. Propensity to enter REM sleep was decreased during treatment compared with baseline and acute discontinuation and the intensity of REM sleep increased during acute discontinuation compared with baseline and treatment. The decrease in dream frequency during SSRI treatment may reflect serotonergic REM suppression while the augmented report length and bizarreness during acute SSRI discontinuation may reflect cholinergic rebound from serotonergic suppression.

KEYWORDS   dreaming, fluvoxamine, paroxetine, serotonin reuptake inhibitors

INTRODUCTION

Clinical lore and a small number of published studies report that the selective serotonin reuptake inhibitors (SSRIs) intensify dreaming. This study examines the dream effects of

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paroxetine and fluvoxamine in order to both increase clinical knowledge of these agents and to test an important potential method for probing the relationship between REM sleep neurobiology and dreaming in humans. This study reports on dream effects in normal subjects associated with the usual starting doses of the commonly prescribed SSRIs paroxetine and fluvoxamine. We examined the dream effects of these two drugs upon acute administration, after initial achievement of steady state plasma levels and upon acute discontinuation. The

effects of these SSRIs on REM sleep were investigated using the Nightcap ambulatory sleep monitor.

As predicted by the reciprocal interaction hypothesis of REM sleep neurobiology (Hobson *et al.* 1975; McCarley and Hobson 1975), cholinergic drugs potentiate REM sleep (Berger and Riemann 1993; Berger *et al.* 1989; Gillin *et al.* 1991; Sitaram *et al.* 1976, 1978a,b) while aminergic drugs, such as serotonin and/or norepinephrine reuptake inhibiting antidepressants, suppress REM (Gaillard *et al.* 1994; Nicholson *et al.* 1989; Sharpley and Cowen 1995; Trivedi *et al.* 1999; Vogel *et al.* 1990). Aminergic antidepressants with anticholinergic properties would be expected to further suppress REM sleep.

Because dreaming is most often reported following awakenings from REM sleep in comparison with other stages of sleep (Hobson *et al.* 2000b; Kahn *et al.* 1997; Nielsen 1999, 2000; Takeuchi *et al.* 1999), the activation synthesis model (Hobson and McCarley 1977) and the Activation, Input Source, Modulation (AIM) extension of the activation synthesis model (Hobson 1990, 1992; Hobson and Stickgold 1994; Hobson *et al.* 1998, 2000b) of dreaming predict that cholinergic drugs should potentiate the frequency of occurrence and/or enhance the characteristic features of dreaming while aminergic drugs should suppress dreaming (Hobson *et al.* 1998, 2000b; Hobson and Stickgold 1994). In fact, cholinergic stimulation has been shown to induce REM sleep with dreaming (Sitaram *et al.* 1978a) and nightmares are associated with cholinesterase inhibitors such as donepizil (Ross and Shua-Haim 1998).

Cholinergic rebound following cholinergic suppression by aminergic drugs may contribute to the intensification of REM sleep and dreaming reported during discontinuation of tricyclic and SSRI antidepressants (Coupland *et al.* 1996; Dilsalver 1994). Discontinuation of aminergic antidepressants results in REM rebound even in the long-half life SSRI fluoxetine (Trivedi *et al.* 1999). Paroxetine and fluvoxamine have the briefest half lives of currently prescribed SSRIs (with means of 21 and 15 h, respectively) and neither have active metabolites (DeVane 1992) while paroxetine is the SSRI showing the most anticholinergic activity (Pollock *et al.* 1998; Richelson 1994). This combination of rapid elimination and, in the case of paroxetine, anticholinergic activity, suggest that discontinuation of these drugs might produce REM sleep and dreaming effects attributable to REM rebound, a condition known to be associated with intensified dreaming and nightmares (Manfridi and Kales 1987). Indeed, paroxetine is the SSRI most often associated with a withdrawal syndrome (Coupland *et al.* 1996).

However, contrary to the simple application of the above predictions, relative enhancement of dreaming has been noted during treatment with the SSRIs fluoxetine (Armitage *et al.* 1995a; Lepkifker *et al.* 1995; Markowitz 1991; Pace-Schott *et al.* 1994, 2000) and citalopram (Koponen *et al.* 1997), while alterations of dream content have been noted with sertraline (Kirschner 1999). Use of paroxetine and fluvoxamine allows the study of this apparently paradoxical SSRI effect without the potentially confounding effects of the long half lives and active metabolites found in fluoxetine and sertraline (DeVane 1992).

Three additional confounds have complicated studies which examined antidepressant effects on dreaming in depressed subjects. First, although depression itself is sometimes associated with shortened REM latency and increased REM density (Berger and Riemann 1993), it is also associated with reduced dream recall compared with normals (Riemann *et al.* 1990). Second, successful antidepressant treatment has been associated with a further slight reduction in dream recall over pretreatment baseline levels (Armitage *et al.* 1995a; Riemann *et al.* 1990) except in the case of fluoxetine (Armitage *et al.* 1995a). And third, as noted above, most antidepressants suppress REM sleep. Therefore, drug effects on dreaming in depressed subjects reflect the complex net result of depression-related dream suppression, a putative recovery-related dream enhancement, depression-related REM enhancement, and drug-related REM suppression. Moreover, it is extremely difficult to separate the relative importance of dream production vs. dream recall effects in such subjective reports.

To minimize these confounding factors, we have studied the effects of paroxetine and fluvoxamine on dreaming in normal volunteers as part of a comparison of the sleep quality effects of these two commonly prescribed SSRIs (Pace-Schott *et al.* 1999, 2000; Silvestri *et al.* 1998, in press). We interpret our results in terms of these drugs' physiological effects on sleep (Digler *et al.* 1995; Kupfer *et al.* 1991; Silvestri *et al.* 1998, in press; Staner *et al.* 1995) and the underlying neuronal control mechanisms of REM sleep (Hobson *et al.* 1998, 2000b; Steriade and McCarley 1990) and dreaming (Hobson *et al.* 1998, 2000a,b). These results constitute preliminary data on a method for probing the relationship between REM sleep neurobiology and dreaming in humans.

METHODS

Participants

Participants were 14 normal paid volunteers (4 males, 10 females; mean age 27.4 year, age range 22–39) recruited by newspaper advertisements. Participants were determined to be free of medical and neuropsychiatric symptoms or treatment with (or admitted current abuse of) psychotropic or sleep affecting drugs. All potential participants were screened by phone and, if no exclusion criteria were noted, came to the laboratory for a psychiatric interview and a physical exam. This study was approved by the Massachusetts Mental Health Center institutional review board and all participants gave written informed consent. Subjects were assigned randomly to receive either fluvoxamine or paroxetine (half receiving each drug) and investigators remained blind as to which subject received which drug until all sleep and dream data had been scored. The current investigation was limited to a small sample size of 14 because it was a pilot study operating on limited funding with large per-subject investment of resources. As the quantitative effects of antidepressant drugs on dreaming are poorly known, no pre-hoc estimates of effect sizes and statistical power for the variables assessed were feasible.

Procedure

The study lasted 31 days and consisted of 7 days baseline, 19 days on either 100 mg fluvoxamine or 20 mg paroxetine (given in divided morning and evening doses), and 5 days acute discontinuation (during which time subjects ceased taking pills altogether). Dosing was begun on day 8 and steady state levels were considered to be well achieved after 10 days treatment (day 18). Although steady state plasma levels were not confirmed by assay, a 10-day time to steady state is based upon the assumption that five half-lives are required to achieve steady state (DeVane 1990) and five half-lives of paroxetine range from 0.8 to 13.3 days with a mean of 4.4 days while five half-lives of fluvoxamine range from 2.7 to 4.0 days with a mean of 3.1 days (computed from DeVane 1992). This experimental design is illustrated in Fig. 1. Subjects' sleep was monitored using the Nightcap ambulatory sleep monitor (Ajilore *et al.* 1995) which was worn nightly during baseline, initial dosing and acute discontinuation and every third night between days 12 and 26 (Silvestri *et al.* 1998, in press). Every morning, subjects completed a sleep quality and dream features questionnaire and wrote a report of any dreams they could recall from the previous night. When a subject recalled more than one distinguishable dream from the same night, each was recorded as a separate dream report.

Dream scoring procedures

Self-ratings by subjects. On mornings when dream(s) were recalled, subjects completed a hand-written dream report and then scored each line of their report for presence and intensity of six emotion categories (fear/anxiety, anger, sadness, shame, joy/elation, affection/erotic) on a scale of 1–5 (5 = highest intensity). More than one emotion category could be chosen for a given line of written report and scoring was facilitated by a lined report form with columns for emotion categories to the right of each line (Merritt *et al.* 1994). After writing reports and scoring emotions line-by-line, subjects completed the sleep

and dream quality questionnaire. The dream questionnaire contained seven 5-point Likert scales (1 = highest) rating the past night's dreaming on dimensions of memorability, visual vividness, amount of sound, amount of movement, emotional intensity, meaningfulness and strangeness.

Scoring of reports by judges. All hand-written reports were typed by an assistant who was not one of the judges and each report was assigned a random number which remained its only identifier until all scoring was complete. Each report was scored by three judges using the following three scales: (1) bizarreness (Hobson *et al.* 1987, as modified in Williams *et al.* 1992), (2) fictive movement (Maher 1997) and (3) visual words, nouns only (Antrobus *et al.* 1977). In order to enhance inter-rater reliability, the three judges first scored ten 5 to 10-dream sample data sets (from Merritt *et al.* 1994) meeting after each set to discuss their decisions. Interrater reliability increased asymptotically over 10 sessions to the following values for at least two judges having identical scores (average of the last five data sets): bizarreness 49%; movement 71%; visual nouns 83% (last four sets).

The typed, randomized reports from all participants were independently scored by the three judges who remained blind to subject identity, drug treatment and Study Phase from which reports were collected until all scoring was complete. Results were then compiled by the three judges who determined the specific items being scored by two or more judges. Only items scored by two or more judges were used in subsequent analyses. Total word counts, rather than 'TRC' (i.e. edited word count with all non-dream-experience describing words removed, Antrobus 1983), were used to measure report length as subjects were instructed to write down only dream content and they complied well with this instruction.

Nightcap measurement of REM parameters. The Nightcap ambulatory sleep monitor (Ajilore *et al.* 1995) was used to obtain estimates of REM latency and eyelid movement density during REM. The Nightcap is a two-channel recording device which distinguishes wake, REM sleep, and non-REM (NREM) sleep (Ajilore *et al.* 1995). One channel of the
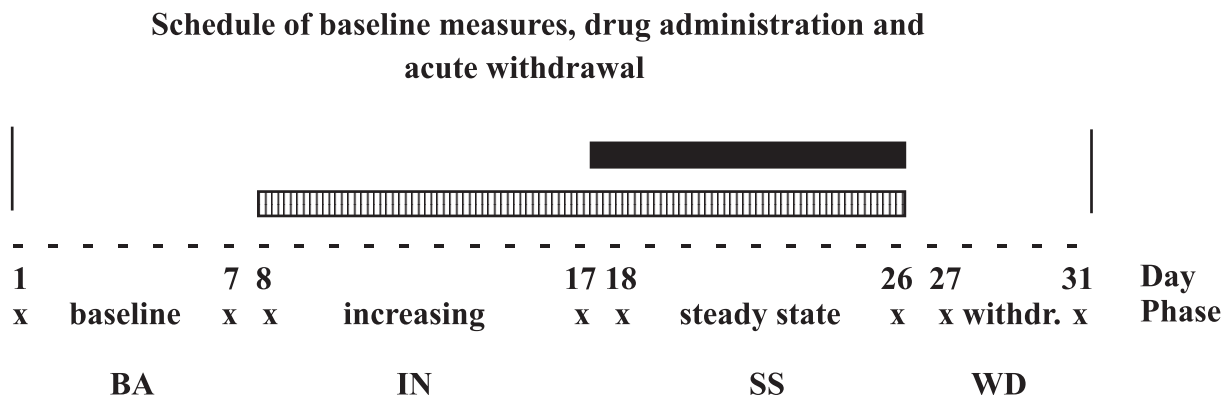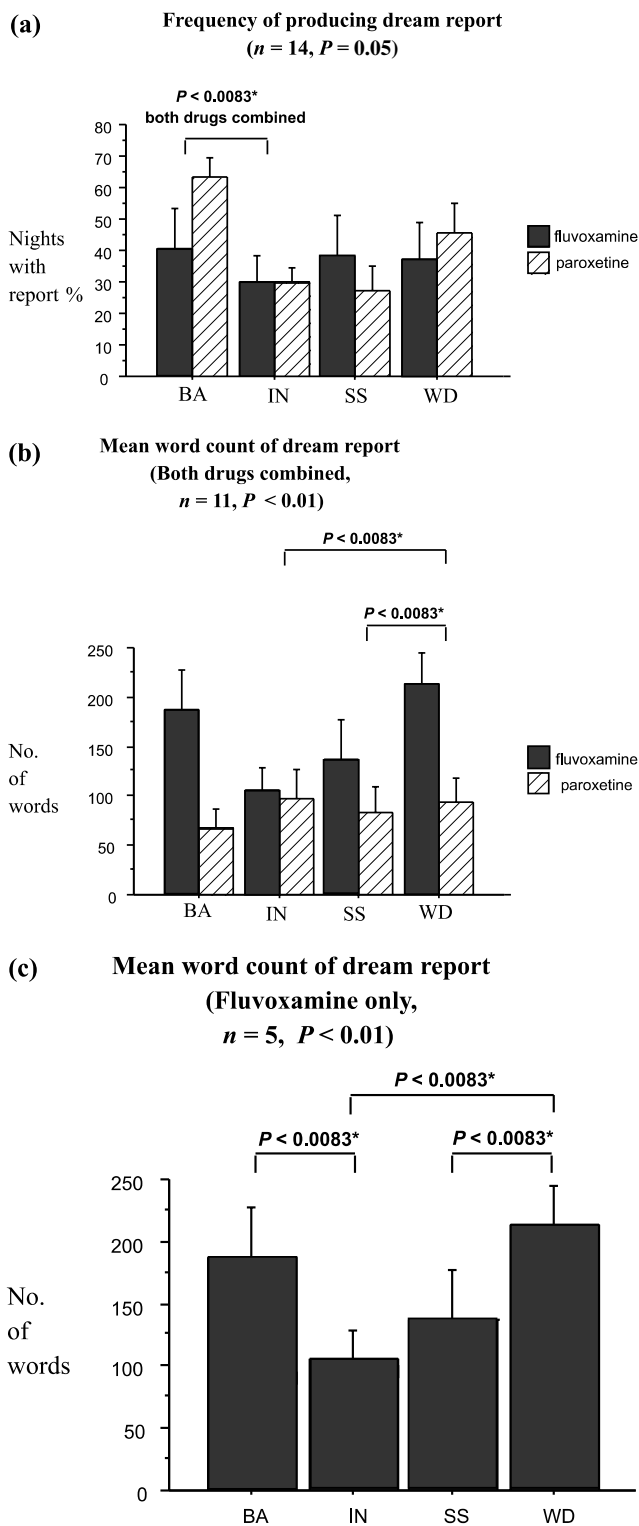
Schedule of baseline measures, drug administration and acute withdrawal

1		**7**	**8**		**17**	**18**	**26**	**27**	**31**	**Day**
x	**baseline**	**x**	**x**	**increasing**	**x**	**x**	**steady state**	**x**	**x withdr.**	**x**	**Phase**
	BA			**IN**			**SS**		**WD**		

Figure 1. Experimental design of current study. The phases of the study were defined as follows: BA = baseline (days 1–7); IN = increasing plasma levels (days 8–17); SS = steady state (days 18–26); WD = acute discontinuation or 'withdrawal' (days 27–31). The upper bar identifies the Steady State Study Phase whereas the lower bar illustrates the entire drug treatment period.

(a)

Frequency of producing dream report
(n = 14, P = 0.05)

(b)

Mean word count of dream report
(Both drugs combined,
n = 11, P < 0.01)

(c)

Mean word count of dream report
(Fluvoxamine only,
n = 5, P < 0.01)

Nightcap monitors eye movement and the other monitors major head movements. The *NC Analyzer* software (Ajilore *et al.* 1995) uses raw per-minute eyelid and head movement counts with a computerized algorithm to score each recorded minute as Wake, REM sleep or NREM sleep.

Figure 2. The effect of Study Phase on dream frequency and report length in 14 normal subjects. (a) Mean frequency of generation of dream reports on a per-night basis. (b) Mean total dream report length for both drugs. (c) Mean total report length for the fluvoxamine treated subjects alone. Significance levels were obtained using Means Comparisons performed in only those ANOVAs where there was a significant main effect for Study Phase (in parentheses below title). Although means and standard errors for both drugs are depicted, the significance levels in brackets refer to the post hoc Means Comparison of Study Phase for both drugs combined in the repeated measures ANOVA with Drug as a factorial. *An alpha level of $P < 0.0083$ was established for the Means Comparisons by a Bonferroni correction for six contrasts (BA vs. IN, BA vs. SS, BA vs. WD, IN vs. SS, IN vs.WD, SS vs. WD) performed per ANOVA. Bars indicate standard error.

Analysis of data

For both subject-rated and judged dream data, four main Study Phases were defined as follows: Baseline (BA) – days 1–7; Increasing plasma levels (IN) – days 8–17; Steady State plasma levels (SS) – days 18–26; and acute discontinuation or 'Withdrawal' (WD) – days 27–31. Dream parameters compared among the four Study Phases (BA, IN, SS & WD) included: dream recall frequency, dream length, seven subject-rated questionnaire items, a total subject-rated emotion score, and judge-determined total bizarreness, total movement and total visual nouns scores. Averages for each parameter, for each subject, in each Study Phase were the raw data entered into analyses. The per-dream value of each parameter was used to compute subject means for each Study Phase. Dream recall frequency was computed as the per-night rate of one or more dreams being recorded.

For dream data, per subject Study Phase means comprised four repeated measures in two-way (Study Phase X Drug) repeated measures analyses of variance (ANOVA) performed individually on each subject-rated and judge-determined dream parameter. For a given subject, any Study Phase in which no dreams were recorded, produced no Study Phase subject mean for that parameter and hence were excluded from the ANOVA thereby reducing N (with the exception of dream recall frequency data where absence of dreams equals zero recall frequency). Means Comparison contrasts were performed between Study Phases only when the univariate ANOVA showed significant variation ($P < 0.05$) of the parameter being analysed associated with the repeated measure (i.e. Study Phase). The alpha-level used for Mean Comparisons ($P < 0.0083$) was Bonferroni adjusted for increased probability of Type I error in six multiple comparisons (BA vs. IN, BA vs. SS, BA vs. WD, IN vs. SS, IN vs.WD, SS vs. WD). Each parameter is described in more detail below.

In the case of Nightcap-measured REM sleep parameters (REM latency and eyelid movements per minute in REM), three main Study Phases were defined as follows: Baseline (BA) – days 1–7; Steady State plasma levels (SS) – days 18–26; and acute discontinuation (WD) – days 27–31 (see Silvestri *et al.* 1998, in press). Per subject Study Phase means comprised

three repeated measures in a two-way (Study Phase X Drug) repeated measures multivariate analysis of variance (MANOVA) of both REM parameters and univariate analyses of variance (ANOVA) performed on each REM measure. The alpha-level used for Means Comparisons ($P < 0.0167$) was Bonferroni adjusted for increased probability of Type I error in three multiple comparisons (BA vs. SS, BA vs. WD, SS vs. WD).

Dreaming and REM sleep parameters

Dream questionnaire self-ratings by subjects. Using only those nights where dreaming was recalled as having occurred (and the seven scales completed), subject means were computed for Likert scale responses for each dimension in each night of a given Study Phase.

Dream report emotion self-ratings by subjects. The subjects' emotion ratings (1–5) assigned to each line of text for each emotion category were summed for each emotion category in each dream. For the current analyses, a combined emotion score was computed for each dream.

Judged scores – bizarreness. The bizarreness scale used (Hobson *et al.* 1987; Williams *et al.* 1992) characterizes each bizarre dream item with a two-digit code which assigns to it one of three loci (dream plot, dreamer's thoughts, dreamer's emotions) and one of three bizarreness types (incongruity, discontinuity, uncertainty) with a fourth-type score (ad-hoc explanation) not assigned a locus. For the current analysis, the data used were the total number of all bizarre events (i.e. all incongruities, discontinuities, uncertainties and ad-hoc explanations) scored as bizarre in any way by two or more judges.

Judged scores – movement. Using the Maher (1997) scale, judges identified and characterized instances of movement by the dreamer and of other dream characters or objects. Only movement scores agreed upon by two or more judges were included in the analyses.

Judged scores – visual nouns. Using only the visual noun category of the Antrobus *et al.* (1977) visual imagery scale, all visual nouns in each dream were identified by the judges. Both individual nouns (e.g. 'the man') and explicitly mentioned aggregates of which they were a member (e.g. 'a crowd of men') were counted as separate nouns. The total number of visual nouns was then determined as the number of nouns agreed upon by two or more judges.

REM latency (RLAT). The values were judge-determined estimates of the number of minutes from sleep onset to the first minute of REM sleep in Nightcap records visually displayed by the *NC Analyzer* software (Ajilore *et al.* 1995). Three investigators (RS, EPS and RS) estimated RLAT for each subject-night (presented in a randomized order) while blind to subject identity, treatment phase and medication. Three-judge averages were used to compute per-subject Study Phase averages.

Eyelid movements per minute in REM (ELM/MIN REM) were defined as a night's average number of eyelid movements in each minute algorithmically scored as REM sleep by the *NC Analyzer* (Ajilore *et al.* 1995).

RESULTS

General characteristics of recorded dreams over all Study Phases

A total of 206 dream reports were collected from the 14 subjects across the 31 days of the study. Subjects reported varying total numbers of dreams over the entire study. One subject apiece reported totals of 1, 4, 6, 14, 19, 24, and 43 dreams, two subjects reported totals of 12 and 16 dreams, respectively, and three subjects reported 13 dreams each (mean 14.7, standard deviation 10.0, median 13). The length of recorded dreams ranged from 1 to 727 words with a mean of 121, a standard deviation of 112 and a median of 88.5. There were only five dreams with less than 10 words, and only 15 dreams with less than 25 words. Among the 14 subjects over the 31 total nights in the protocol, the number of nights at least one dream was recorded ranged from 1 (3.2% of 31 total nights) to 26 (83.9%) with a mean of 11.7 (37.8%), a standard deviation of 5.9 (19.0%) and a median of 12 (38.7%). Eight of the 14 subjects recorded only one dream per night with reports (79.2% of 164 total subject/nights with reports), six had at least one night with two dreams recorded (20.7% of total subject/nights), and five had at least one night with three or more dreams recorded (8.5% of total subject/nights). This extreme variability in the dream reporting capacity of our subjects decreased the likelihood that statistically significant measures would emerge from these data. Nevertheless, several of our measures showed statistically significant differences among Study Phases and showed consistent patterns of change as detailed below.

Effect of Study Phase: self-report questionnaire data

The seven Likert scale self-report responses (Fig. 3a–e) showed an overall tendency for dreams to become more intense on several dimensions during the later Study Phases (SS and WD) compared with earlier Study Phases (BA and IN). Over the four Study Phases, univariate ANOVAS showed significant increase ($P < 0.05$) in subject-rated dream memorability, visual vividness, amount of sound, emotional intensity and meaningfulness. (These significant results could not be attributed to 'outlier' subject responses because among the memorability, vividness, sound, emotional intensity, and meaningfulness scales, nine of 13 subjects rated greatest intensity during SS, WD or both and there was no relationship between the number of scales showing this pattern for a subject and the overall number of dreams he or she recalled.) No significant Study Phase differences were seen in Likert scale ratings of movement, or strangeness. There were no significant main effects for Drug and no Drug X Study Phase interactions for any of the Likert scales. Table 1 shows the per Study Phase means for the drug groups individually and pooled.

Memorability. On the Likert rating scales, subjects rated dreams significantly more memorable (Fig. 3a) during WD compared with IN ($P < 0.0083$). The increases in
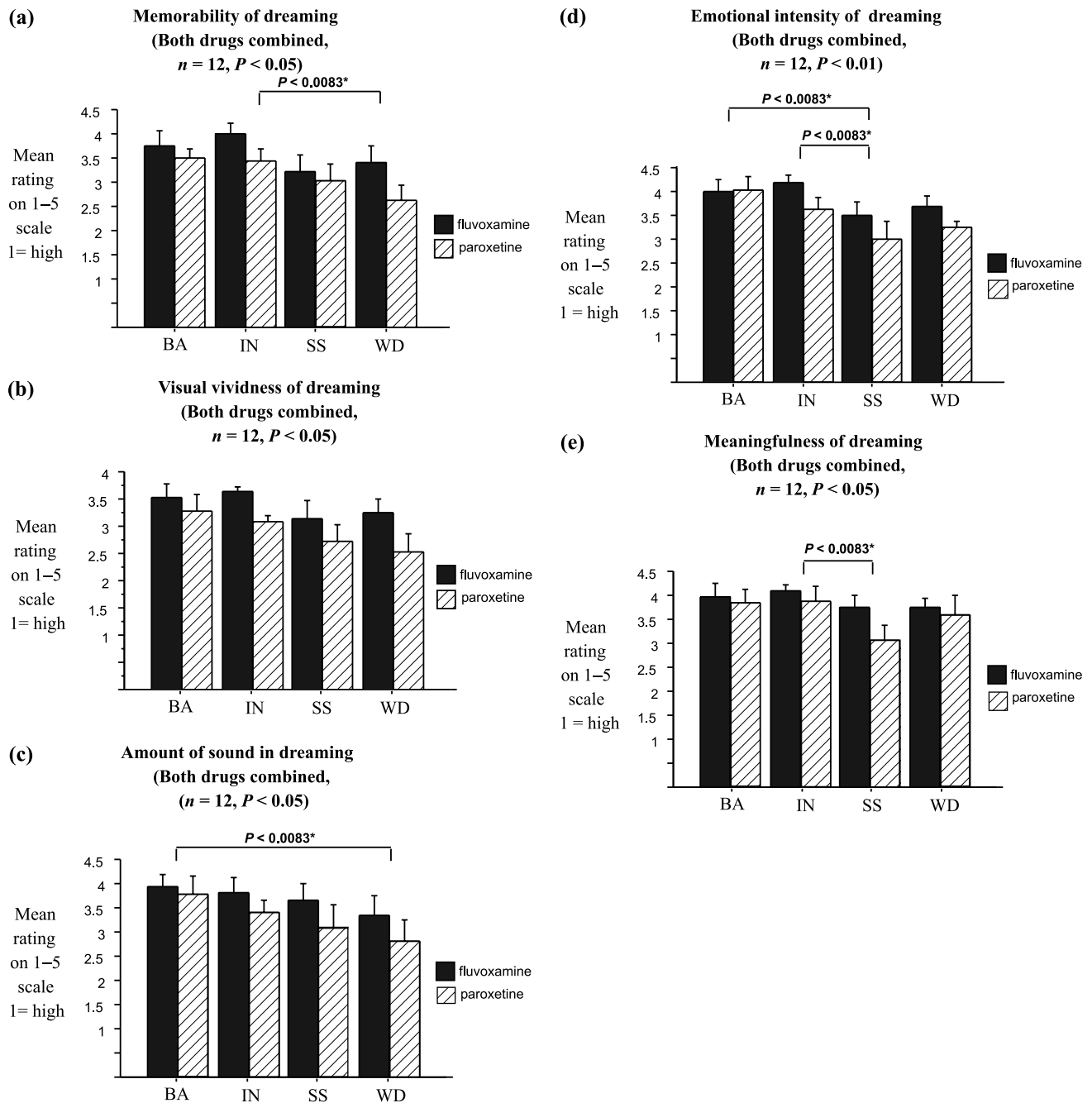
Figure 3. The effect of Study Phase on nightly subject-ratings of dream qualities using a 5-point (1–5) scale (1 = highest) on a per-night basis. (a) Mean subject-rated memorability of dreaming (How memorable was your dreaming? Most memorable ever = 1, only remember dreaming = 5). (b) Mean subject-rated visual vividness of dreaming (How visually vivid was your dreaming? Most vivid ever = 1, not at all vivid = 5). (c) Mean subject-rated amount of sound in dreaming. (How much sound [e.g. voices] was in your dreaming? Most sound ever = 1, no sound = 5). (d) Mean subject-rated emotional intensity of dreaming (How emotionally intense was your dreaming? Most intense ever = 1, not at all intense = 5). (e) Mean subject-rated meaningfulness of dreaming (How meaningful was your dreaming? Most meaningful ever = 1, not at all meaningful = 5). No significant phase of study effects were seen for dream movement (How much movement was in your dreaming? Most movement ever = 1, no movement = 5), or strangeness (How strange or weird your dreaming felt, most strange ever = 1, not at all strange = 5). The phases of the study and statistical measures are as indicated for Fig. 2.

memorability from BA to SS and to WD were present as trends ($P = 0.047$ and $P = 0.0182$, respectively) with effect sizes in the medium ($0.50 <$ effect size < 0.80) and large (effect size > 0.80) ranges (0.69 and 0.82, respectively) sug-

gesting that, with a larger sample size, there would be sufficient statistical power to achieve significance (Lipsey and Wilson 2000). (Effect size of differences between two means with equal sample sizes equals the difference between the means divided

Table 1 Per Study Phase means, standard deviations (in parentheses) and sample size (;N) for all variables for both drug groups pooled and for groups individually. (Sample sizes vary because ANOVA analyses eliminated missing cells.) See Figures 2, 3 and 5 for Study Phase main effects and post-hoc Means Comparisons between Study Phases

Study Phase variables	BA	IN	SS	WD
Both drugs				
Objective				
1. Frequency	0.520 (0.278); 14	0.300 (0.166); 14	0.325 (0.284); 14	0.414 (0.277); 14
2. Word count	122 (92); 11	101 (61); 11	108 (76); 11	148 (86); 11
Judged				
3. Bizarreness	3.16 (1.83); 10	3.17 (2.34); 10	3.10 (2.60); 10	5.32 (3.68); 10
4. Normal biz.	0.025(0.014); 11	0.025 (0.011); 11	0.021 (0.011); 11	0.030 (0.013); 11
5. Movement	3.28 (3.77); 11	2.86 (1.77);11	3.01(2.33);11	4.13(3.16);11
6. Visual nouns	9.54 (7.57); 11	8.72 (6.67); 11	8.46 (6.01); 11	10.75 (5.67); 11
7. Emotion	25.99 (19.70); 8	17.66 (12.90); 8	27.65 (25.30); 8	32.17 (30.59); 8
Likert scale 1–5				
8. Memorability	3.626 (0.607); 12	3.712 (0.630); 12	3.127 (0.815);12	3.025 (0.845); 12
9. Vividness	3.401 (0.674); 12	3.356 (0.387); 12	2.93 (0.796); 12	2.877 (0.803); 12
10. Sound	3.858 (0.772); 12	3.596 (0.722); 12	3.379 (1.00); 12	3.068 (1.06); 12
11. Emot. Intense	4.009 (0.638); 12	3.913 (0.569); 12	3.259 (0.801); 12	3.465 (0.475); 12
12. Meaningful	3.900 (0.663); 12	3.986 (0.531); 12	3.417 (0.746); 12	3.665 (0.754); 12
13. Movement	3.458 (0.774); 12	3.311 (0.643); 12	3.215 (0.705); 12	2.992 (0.808); 12
14. Strangeness	3.966 (0.645); 12	3.442 (0.574); 12	3.719 (0.629); 12	3.671 (0.965); 12
Fluvoxamine				
Objective				
1. Frequency	0.408 (0.334); 7	0.300 (0.216); 7	0.381 (0.351); 7	0.371 (0.315); 7
2. Word count	187 (92); 5	105 (50); 5	138 (88); 5	213 (70); 5
Judged				
3. Bizarreness	4.29 (1.95); 5	2.93 (2.15); 5	3.20 (3.05); 5	7.17 (3.98); 5
4. Normal biz.	0.025 (0.006); 5	0.024 (0.012); 5	0.021 (0.009); 5	0.033(0.012); 5
5. Movement	5.37 (4.88); 5	3.12 (2.51); 5	3.68 (2.64); 5	4.89 (4.30); 5
6. Visual nouns	13.3 (9.00); 5	6.97 (3.02); 5	10.38 (6.12); 5	11.73 (4.83); 5
7. Emotion	33.02 (20.85); 5	14.82 (11.06); 5	32.50 (30.03); 5	35.28 (39.36); 5
Likert scale 1–5				
8. Memorability	3.743 (0.773); 6	3.993 (0.519); 6	3.225 (0.838); 6	3.417 (0.810); 6
9. Vividness	3.535 (0.580); 6	3.627 (0.256); 6	3.133 (0.854); 6	3.238 (0.653); 6
10. Sound	3.928 (0.655); 6	3.798 (0.785); 6	3.655 (0.846); 6	3.337 (1.012); 6
11. Emot. Intense	3.990 (0.642); 6	4.202 (0.380); 6	3.510 (0.648); 6	3.675 (0.555); 6
12. Meaningful	3.967 (0.666); 6	4.083 (0.315); 6	3.760 (0.614); 6	3.747 (0.440); 6
13. Movement	3.695 (0.558); 6	3.525 (0.683); 6	3.217(0.698); 6	3.450(0.578); 6
14. Strangeness	3.968 (0.669); 6	3.535 (0.633); 6	3.785 (0.733); 6	3.903 (0.863); 6
Paroxetine				
Objective				
1. Frequency	0.633 (0.162); 7	0.300 (0.115); 7	0.270 (0.211); 7	0.457 (0.251); 7
2. Word count	67 (48); 6	97 (73); 6	84 (62); 6	94 (57); 6
Judged				
3. Bizarreness	2.02 (0.735); 5	3.41 (2.74); 5	2.99 (2.43); 5	3.48 (2.49); 5
4. Normal biz.	0.024 (0.018); 6	0.026 (0.011); 6	0.021 (0.013); 6	0.028 (0.014); 6
5. Movement	1.54 (1.13); 6	2.65 (1.06); 6	2.45 (2.11); 6	3.43 (1.99); 6
6. Visual nouns	6.40 (4.87); 6	10.18 (8.72); 6	6.86 (5.97); 6	9.93 (6.63); 6
7. Emotion	14.27 (12.60); 3	22.40 (16.84); 3	19.56 (16.67); 3	26.98 (10.63); 3
Likert Scale 1–5				
8. Memorability	3.508 (0.425); 6	3.430 (0.642); 6	3.028 (0.858); 6	2.633 (0.739); 6
9. Vividness	3.267 (0.786); 6	3.085 (0.296); 6	2.717 (0.749); 6	2.517 (0.838); 6
10. Sound	3.787 (0.934); 6	3.393 (0.657); 6	3.103 (1.144); 6	2.800 (1.119); 6
11. Emot. Intense	4.028 (0.695); 6	3.625 (0.607); 6	3.008 (0.917); 6	3.255 (0.289); 6
12. Meaningful	3.833 (0.717); 6	3.888 (0.706); 6	3.075 (0.751); 6	3.583 (1.021); 6
13. Movement	3.220 (0.934); 6	3.097 (0.577); 6	3.213 (0.778); 6	2.533 (0.774); 6
14. Strangeness	3.963 (0.683); 6	3.350 (0.552); 6	3.653 (0.569); 6	3.438 (1.083); 6

by the the square root of the average of the two means' standard deviations squared, Lipsey and Wilson 2000.)

Visual vividness. The increases in visual vividness from BA to SS and to WD were present as trends ($P = 0.0397$ and $P = 0.0247$, respectively) both with medium effect sizes of 0.650.71, respectively (Fig. 3b).

Sound. Subjects rated dreams as having significantly more sound (Fig. 3c) during WD compared with BA ($P < 0.0083$). The increases in subject rated sound from BA to SS was present as a trend ($P = 0.0445$) with a medium effect size (0.53).

Emotional intensity. Dreams were rated significantly more emotionally intense (Fig. 3d) during SS compared with BA and IN ($P < 0.0083$) as well as a trend ($P = 0.0252$) with a large effect size (.97) for greater emotional intensity during WD compared with BA.

Meaningfulness. Subjects rated dreams significantly more meaningful (Fig. 3e) during SS compared with IN ($P < 0.0083$) as well as a trend ($P = 0.017$) with a medium effect size (0.68) for greater meaningfulness during SS compared with BA.

When subject ratings on dream intensity Likert scales with significant Study Phase main effects were regressed against objective dream measures (recall frequency, word count) across subjects within each Study Phase, no consistent pattern of significant correlations emerged. Although there was a tendency for greater memorability and vividness with increased recall frequency in the BA Study Phase ($P = 0.009$ and 0.0212, respectively), the significance of these probabilities does not survive correction for numerous (40) repeated correlation analyses (Howell 1997) and the remaining correlation coefficients were low indicating small effect sizes.

As discussed below, the treatment and acute discontinuation-related intensification of dreaming may be related to REM rebound phenomena. Evidence for REM suppression during treatment followed by REM rebound phenomena during WD is provided by the finding of significantly longer REM latency during SS compared with BA (Fig. 4a) and greater eyelid movement density in REM during WD compared with both BA and SS (Fig. 4b).

Effect of Study Phase: dream reports

Figure 2a shows that the mean per night frequency of producing a written dream report among the 14 subjects: (i) varied significantly (ANOVA) across the Study Phases ($P < 0.05$) (ii) was significantly greater during BA as compared with IN ($P < 0.0083$) (iii) was almost significantly greater during BA as compared with SS ($P = 0.009$; effect size = 0.69); and, iv. returned to near BA level during WD. ANOVA revealed no significant main effects for Drug or Drug X Study Phase interaction in dream report frequency. (See Table 1 for means and standard deviations.)

Figure 2b shows that the average per subject dream report length: (i) varied significantly across the Study Phases ($P < 0.01$); (ii) was significantly greater ($P < 0.0083$) during

WD compared with IN and SS; and (iii) tended ($P < 0.05$) to be longer in WD compared with BA ($P = 0.039$, effect size = 0.30) and in BA compared with IN ($P = 0.0461$; effect size = 0.27). The fluvoxamine-treated subjects showed a trend toward higher average word count across all Study Phases ($P = 0.0816$; effect size = 1.06) compared with the paroxetine-
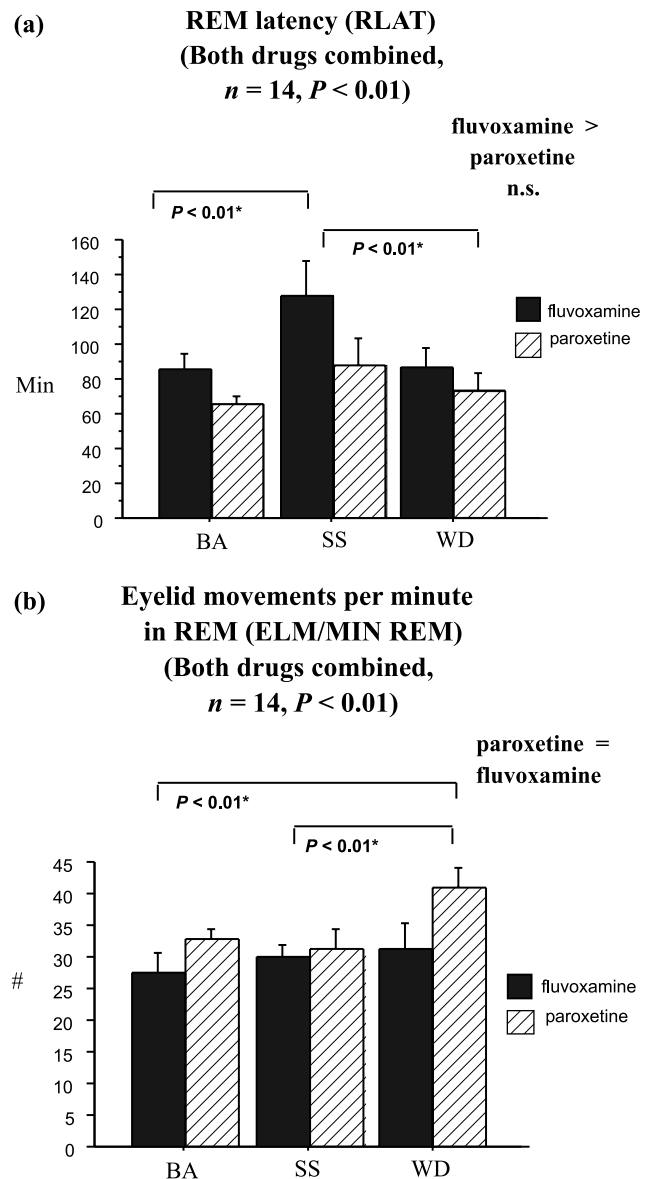

(a)   REM latency (RLAT)
(Both drugs combined,
$n = 14$, $P < 0.01$)

fluvoxamine >
paroxetine
n.s.

$P < .01*$ $P < .01*$

■ fluvoxamine
▨ paroxetine

Min   BA   SS   WD

(b)   Eyelid movements per minute
in REM (ELM/MIN REM)
(Both drugs combined,
$n = 14$, $P < 0.01$)

paroxetine =
fluvoxamine

$P < .01*$ $P < .01*$

■ fluvoxamine
▨ paroxetine

BA   SS   WD

Figure 4. Variation between Drugs and across Study Phases in two measures of REM intensity computed from Nightcap data (see Methods for definitions of measures). (a) REM Latency. (b) Eyelid movements per minute in REM. The phases of the study were defined as follows: BA = baseline (days 1–7); SS = steady state (days 18–26); WD = acute discontinuation (days 27–31). Significance levels were obtained using Means Contrasts performed in only those ANOVAs where there was a significant main effect for Study Phase (in parentheses below title). *An alpha level of $P < 0.0167$ was established for the Means Comparisons by a Bonferroni correction for three contrasts (BA vs. SS, BA vs. WD, SS vs. WD) performed per ANOVA. Bars indicate standard error.

treated subjects and there was a significant Drug X Study Phase interaction ($P < 0.001$) for word count with the fluvoxamine-treated subjects accounting for the overall increase in word count during WD (Fig. 2b). The primary importance of the fluvoxamine subjects in word count effects (see Fig. 2c) is apparent by comparing univariate one-way repeated measures ANOVAS for the fluvoxamine-treated subjects alone (Study Phase main effect, $P < 0.01$; WD > IN, $P < 0.0083$; WD > SS, $P < 0.0083$; BA > IN, $P < 0.0083$ (Fig. 2c)) with the seven paroxetine-treated subjects alone (Study Phase main effect only a trend, $P < 0.1$). (See Table 1 for means and standard deviations.)

The total number of bizarre items (Fig. 5a) varied significantly across the Study Phases ($P < 0.01$). There were significantly greater ($P < 0.0083$) total numbers of bizarre items in WD as compared with the other three phases (Fig. 5a). There was no significant main effect for drug in bizarreness, however, there was a significant Drug X Study Phase interaction ($P < 0.01$) with the fluvoxamine-treated subjects accounting for the increase bizarreness during WD. The primary importance of the fluvoxamine subjects in the WD-related bizarreness increase (see Fig. 5b) is apparent by comparing univariate one-way repeated measures ANOVAS for the five fluvoxamine-treated subjects alone (Study Phase main effect, $P < 0.01$; WD > BA, $P < 0.05$ trend; WD > IN, $P < 0.0083$; WD > SS, $P < 0.0083$) with the seven paroxetine-treated subjects alone (Study Phase main effect n.s.).

The ANOVA Study Phase main effect remained a trend ($P = 0.0941$) for the fluvoxamine group (see Fig. 5c) even when total bizarreness scores were normalized for report length ('Normalized Bizarreness'). Post-hoc Means Comparisons showed this trend to be present in the comparison of Normalized Bizarreness during WD compared with BA ($P = 0.0967$ with a large effect size of 0.84), IN ($P = 0.0688$, medium effect size 0.75) and SS ($P = 0.0185$, large effect size 1.13). These medium and large effect sizes suggest that, with a larger sample size, there would be sufficient statistical power to achieve significance (Lipsey and Wilson 2000).

There were no significant Study Phase or Drug main effects in movement, visual nouns or total subject-rated emotion. See Table 1 for means and standard deviations.

(a) Mean total number of bizarre items (Both drugs combined, $n = 11$, $P < 0.01$)

(b) Mean total number of bizarre items (Fluvoxamine only, $n = 11$, $P < 0.01$)

(c) Normalized Bizarreness (Fluvoxamine only, $n = 5$, $P = 0.0941$)

Figure 5. The effect of Study Phase on judge-scored dream bizarreness (Williams *et al*. 1992). (a) Mean total number of bizarre items (incongruities + discontinuities + uncertainties + ad-hoc explanations) in dream reports. (b) Mean total number of bizarre items in the five fluvoxamine-treated subjects who reported dreams in all four Study Phases. (c) Mean number of bizarre items divided by word count in the five fluvoxamine-treated subjects. The phases of the study and statistical measures are as indicated for Fig. 2.
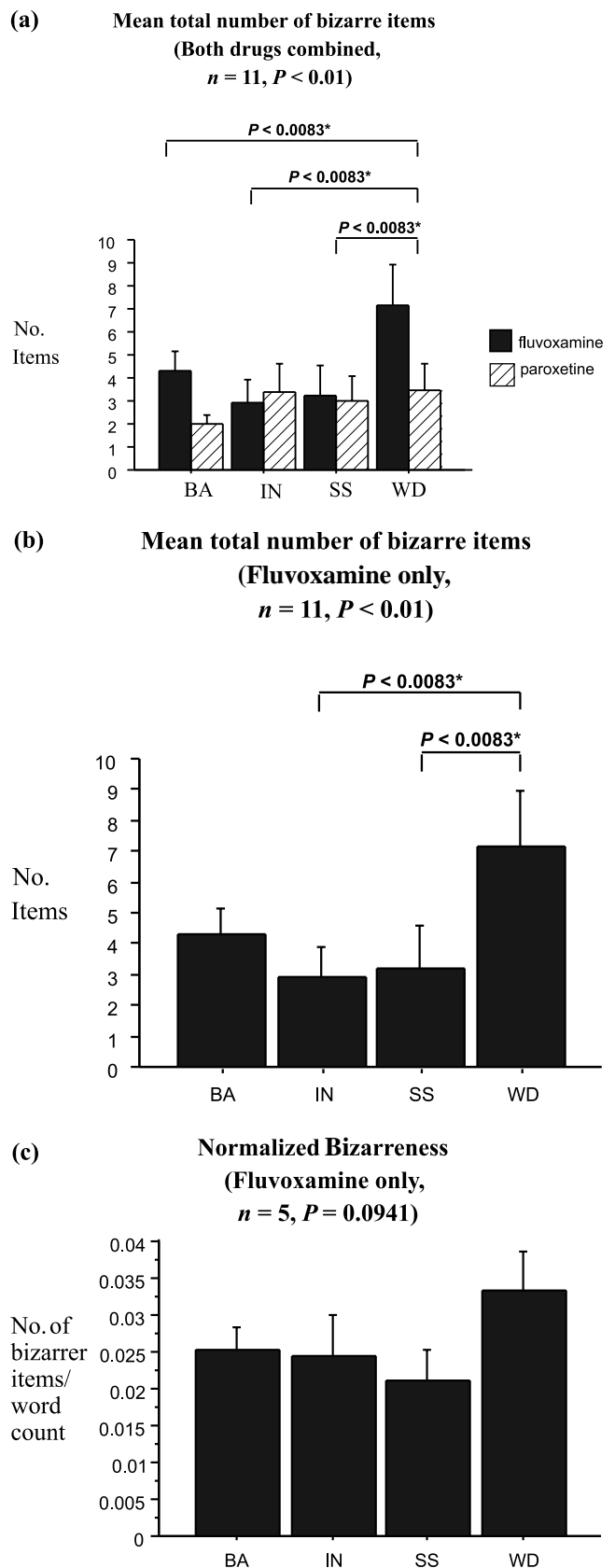
REM-Related Changes Over Baseline, Steady State and Acute Discontinuation.

A MANOVA computed for ELM/MIN REM and RLAT together showed a significant Study Phase main effect ($P < 0.015$) but no Drug main effect or Study Phase Drug interaction. Univariate ANOVAS showed significant Study Phase main effects ($P < 0.01$) for RLAT (Fig. 4a) and ELM/MIN REM (Fig. 4b) and trends ($P < 0.10$) toward significance for a Drug main effect in RLAT (fluvoxamine > paroxetine) and a Drug X Study Phase interaction in ELM/MIN REM (paroxetine effect > fluvoxamine effect). Post-hoc means comparisons for Study Phase showed significantly ($P < 0.01$) higher RLAT in SS compared with BA and WD with a stronger effect for fluvoxamine (Fig. 4a). Post-hoc means comparisons for Study Phase showed significantly ($P < 0.01$) higher ELM/MIN REM in WD compared with both BA and SS with a stronger effect for paroxetine (Fig. 4b). For more details, see Silvestri *et al.* (in press).

DISCUSSION

Using spontaneous dream reporting by normal individuals in the home setting, we have found that treatment with the commonly prescribed starting doses of the SSRIs paroxetine and fluvoxamine results in the following changes in dreaming:

1 Mean dream recall frequency was decreased during periods of drug treatment compared with pre-drug baseline and acute discontinuation.

2 Subject ratings of five out of seven intensity-related characteristics of dreaming (memorability, visual vividness, amount of sound, emotional intensity and meaningfulness) were greater during steady state drug treatment and acute discontinuation as compared with predrug baseline and early drug treatment. The intensity ratings did not consistently correlate with dream recall frequency or word count suggesting that the physiological processes underlying these two types of SSRI effects on dreaming may differ.

3 Mean dream length was greater during acute discontinuation as compared with both pre-drug baseline and drug-treatment periods in fluvoxamine but not in paroxetine-treated subjects.

4 The total number of bizarre items were greatest during acute discontinuation as compared with pre-drug baseline or drug-treatment periods. Significant acute discontinuation-related bizarreness effects were seen in fluvoxamine but not paroxetine-treated subjects. This remained a trend when a number of bizarre items was adjusted for report length in fluvoxamine-treated subjects.

5 A measure of propensity to enter REM sleep (REM latency) was diminished during treatment (especially for fluvoxamine-treated subjects) while a measure of REM sleep intensity (eyelid movements per minute in REM) increased during acute discontinuation (especially for paroxetine-treated subjects).

Over the same period that dream data were being collected from these subjects, Nightcap monitoring showed that objective sleep quality was significantly disrupted by treatment with both paroxetine and fluvoxamine (Silvestri *et al.* 1998, in press). Degraded sleep quality during treatment was indicated by lower sleep efficiency, lower nocturnal eyelid quiescence ('Zip Time' or 'Eyelid Quiescence Index', see Pace-Schott *et al.* 1995; Silvestri *et al.* 1998, in press), lower 'rhythmicity' (a judge-based measure of regularity in Nightcap-displayed sleep architecture, Silvestri *et al.*, in press), as well as higher eyelid movements per min in NREM (Silvestri *et al.* 1998, in press) as well as by a higher number of awakenings (Silvestri *et al.* 1998, in press). Overall, paroxetine disrupted sleep more than fluvoxamine and paroxetine-induced sleep disruption persisted into the acute drug discontinuation phase (Silvestri *et al.*, in press).

We propose the following preliminary interpretations of these results:

1 The decrease in dream frequency during SSRI treatment may reflect serotonergic REM suppression. As noted above (Introduction), considerable evidence suggests that serotonergic and noradrenergic neuromodulation inhibits REM sleep (in part by anticholinergic mechanisms) and that antidepressant drugs (such as the SSRIs) which potentiate aminergic neurotransmission universally suppress human REM sleep. During the present study, REM latency was prolonged during treatment compared with predrug baseline and acute discontinuation especially in fluvoxamine-treated subjects.

2 The augmented word count and bizarreness during acute SSRI discontinuation may reflect cholinergic rebound from serotonergic suppression following discontinuation of short-acting SSRIs. Cholinergic stimulation potentiates REM sleep and discontinuation of aminergic antidepressants result in REM rebound, a condition often associated with intensified dreaming. REM suppression has been reported for both acute and chronic treatment with paroxetine (Digler *et al.* 1995; Staner *et al.* 1995) and fluvoxamine (Kupfer *et al.* 1991) and given their short half lives, their lack of active metabolites, and, for paroxetine, its anticholinergic activity (Richelson 1994), REM rebound would be expected following their discontinuation. In the current study, a measure of REM intensity, eyelid movements per minute in REM (ELM/MIN REM), was indeed increased in acute discontinuation compared with pre-drug baseline and drug treatment. Increases in this eyelid measure can be attributed to increased REM intensity (as indexed by eye movement intensity) because Nightcap-detected eyelid movements reflect underlying REMs (Stickgold *et al.* 1996) and because the eyelid is innervated by portions of the oculomotor complex (Porter *et al.* 1989).

3 The enhancement of subject-rated intensity measures during later drug treatment (in spite of decreased recall frequency) may reflect enhanced global and/or regional brain arousal associated with aminergic stimulation. A possible dissociation between dream initiation processes and the intensification of already occurring dreaming (or its recall) must be considered (see Hobson and Pace-Schott 1999). For example, despite

prolonging REM latency, the SSRI fluoxetine has been shown to increase phasic REM activity (Nofzinger *et al.* 1995). The activating effects of the SSRIs are reflected by their well known alerting and sleep disruptive effects such as increased sleep latency and increased wake time as well as decreased sleep efficiency (Gaillard *et al.* 1994; Nicholson *et al.* 1989; Thase 1998). Acute sleep disruptive effects have been reported for both fluvoxamine (Kupfer *et al.* 1991) and paroxetine (Oswald and Adams 1986; Saletu *et al.* 1991). In the current study, these SSRIs produced such effects in Nightcap-measured sleep efficiency, number of awakenings, nocturnal eyelid quiescence, NREM eyelid movement density and sleep architecture (Silvestri *et al.* 1998, in press). Moreover, chronic sleep disruption accompanying treatment with the SSRI fluoxetine includes additional physiological signs of CNS activation such as: increased fast frequency and decreased delta activity in NREM sleep (Armitage *et al.* 1995b,c; Dorsey *et al.* 1996). There is evidence that drugs which increase CNS arousal by aminergic action can intensify dreaming, a prime example being the intensified dreaming and nightmares associated with L-DOPA treatment (for reviews see Hobson and Pace-Schott 1999; Thompson and Pierce 1999). Alternatively, enhanced subjective dream intensity during treatment may result from late-night cholinergic rebound following early night seroton-ergic REM suppression. Thase (1998) has recently suggested that the combination of increased REM phasic activity and a shifting of overall total REM time closer to morning awaken-ing may underlie reports of intensified dreaming during antidepressant therapy.

4 Drug differences on dreaming may result from their differ-ential effects on sleep quality. Paroxetine's lesser discontinu-ation effects on dream length and bizarreness may be secondary to its greater disruption of sleep continuity com-pared with fluvoxamine during the discontinuation (WD) Study Phase (Silvestri *et al.*, in press). Such sleep disruption by paroxetine may cause micro and macroarousals which inter-fere with the full development of dream plots especially during late night REM periods.

Three additional factors – sleep architecture changes, dream recall effects and specific regional serotonergic brain influences – may also aid in the interpretation of these results.

Sleep architecture. A possible correlate of concurrent dream frequency suppression and dream intensification during SSRI treatment is a de-differentiation of REM/NREM stages. For example, fluoxetine has been shown to produce a profound increase in eye movements during NREM sleep (Armitage *et al.* 1995a; Dorsey *et al.* 1996; Schenck *et al.* 1992). In the current study, such de-differentiation was suggested by a significant disruption of the regular REM/NREM ultradian sleep architecture (as measured by a standardized sleep 'rhythmicity' scale for Nightcap data) during drug treatment as compared with baseline and acute discontinuation (Silvestri *et al.* submitted). Nielsen (1999, 2000) has recently hypothes-ized that sleep disruptive drugs may cause dissociated REM physiological signs to intrude upon NREM sleep ('covert REM sleep') and elicit dream-like NREM mentation.

Dream recall. Opposing effects of serotonin on dream generation (decreased via REM suppression) and dream recall (enhanced via serotonergic neuromodulation) may also underlie the seemingly paradoxical co-occurrence of decreased dream recall frequency but enhanced intensity of recalled dreaming during SSRI treatment. The forgetting of a large proportion of the dreaming which has actually occurred is now considered to be an established fact (Goodenough 1991). Modern models of dream recall suggest that the consolidation of a dream memory trace occurs via a rapid transfer from short-term to long-term memory storage which is, in turn, dependent on the level of arousal immediately following waking – a process which becomes impaired at low levels of arousal (Goodenough 1991). The enhanced dream intensity in persons treated with SSRIs may therefore result from greater recall of preawakening oniric experience because of lighter pre-awakening sleep, greater post-awaken-ing level of arousal, and/or serotonergically enhanced episodic memory.

Regional serotonergic brain influences. SSRIs may alter the serotonergic modulation of specific subcortical-prefrontal circuits which are known to subserve general cognitive behavioral functions and their associated disorders (see Salloway *et al.* 1997). These circuits are known to receive particularly dense projections of serotonergic fibers in primates (Jacobs and Azmita 1992; Wilson and Molliver 1991), to be activated in REM sleep (Braun *et al.* 1997; Nofzinger *et al.* 1997), and have been hypothesized to subserve many of the distinctive features of dreaming (Hobson *et al.* 1998, 2000a,b).

LIMITATIONS AND CONCLUSIONS

The current experiment constitutes a preliminary probe into the dream effects of serotonergic drugs. At least seven limitations with the current analyses limit the conclusions drawn from these data.

1 An important limitation of the current study is the fact that a placebo control group was not run through the same prtotocol as the drug treated groups so that it cannot be conclusively ruled out that some of the late treatment (SS) and acute discontinuation (WD) associated intensification of dreaming could have resulted from increased time on study with an attendant increased skill in recalling dream experience. Two observations, however, argue against the importance of this last potential confound: First, dream recall frequency decreased rather than increased from BA to drug treatment (IN and SS) Study Phases. Second, the paroxetine group did not display the increase in word count and bizarreness in WD compared with the other Study Phases but showed the same overall pattern of increased dream intensity during WD as did the fluvoxamine-treated group (see Fig. 3). Future studies should utilize placebo controls both to address the above concerns and to eliminate any potential confound resulting from subjects being aware that they are discontinuing medi-cation.

2 Despite randomized assignment of subjects to fluvoxamine and paroxetine treatment groups, the BA, pre-treatment mean dream report word count was significantly lower in the paroxetine vs. the fluvoxamine group. However, rather than increasing the liklihood of Type 1 error, the lower word count in the paroxetine group at BA can only make the Study Phase main effect and means differences more conservative. This is because the paroxetine data alone showed no significant changes with Study Phase in contrast to the fluvoxamine group in which there was a significant Study Phase effect on word count among the five fluvoxamine-treated subjects having dreams in each Study Phase (Fig. 2c). Therefore, when data from the two groups are combined, the lower BA word count in the paroxetine group would tend to diminish rather than augment the Study Phase main effect and BA vs. treatment (IN and SS) means differences. Similarly, the relatively constant mean word count of the paroxetine group across IN, SS and WD would tend to diminish rather than augment the significant differences seen between treatment and WD means in the fluvoxamine group.

3 The sample size was low and the intersubject variability in the variables analysed was high. However, the primary statistical effect of low sample size and high intersubject variability is to make the achievement of statistically significant results more rather than less difficult. Despite these constraints, we report conceptually consistent and robustly significant Study Phase differences.

4 Some of the subjects produced so low a number of reports that their data may not have been representative of normal dream reports. In future studies, subjects with predetermined levels of average dream recall might be assigned in a random, blind but balanced manner to different drug treatments so as to minimize this source of inter-subject variability.

5 The cognitive effects of SSRI-induced sleep disruption need to be dissociated from their dreaming effects.

6 Mnemonic or motivational constraints imposed by hand-writing dream reports may have constrained report quality and/or quantity.

7 Nightcap-based measures of REM-latency and REM intensity are still under investigation and the observations of prolonged REM latency during treatment and increased eyelid movement during acute discontinuation would be strengthened by simultaneous polysomnographic recording especially during the crucial late-night preawakening period.

These limitations can be addressed in future studies by modifications of the protocol. For example, investigators should link each individual spontaneous dream report to its preawakening sleep stage using the Nightcap in the home (Stickgold *et al.* 1994) or by polysomnography in the laboratory. Reports should be dictated to audiotape rather than hand written. Finally, instrumental awakenings from specified sleep stages would provide helpful data for comparison with spontaneous reports. These could be performed in the home using the Nightcap (Stickgold *et al.* 1998) or in the home or laboratory by polysomnographic techniques which provide a more detailed profile of pre-report sleep physiology. Despite

such limitations, the current study provides support for current psychophysiological models of dream generation which emphasize the key role of neuromodulatory factors in addition to brain activation and informational input in the differentiation of conscious states.

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