Incidence of Sexual Side Effects in Refractory Depression During Treatment With Citalopram or Paroxetine

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Objective: The incidence of sexual dysfunction due to antidepressant drugs reported in premarketing clinical efficacy trials is often several times lower than in subsequent clinical experiences and independent reports. Although it is commonly believed that the reason for this discrepancy is that the nonleading questions employed in conventional clinical trials underestimate sexual dysfunction while the direct questioning used in independent trials provides more accurate data, few studies have actually compared these 2 methods.

Method: In this study, 119 patients with a DSM-IV–defined major depressive episode (82 women and 37 men) who had been treated with but not responded to a selective serotonin reuptake inhibitor (SSRI; either citalopram or paroxetine) were assessed regarding sexual functioning by means of open-ended questions and direct questioning at baseline (after SSRI treatment only) and after 4 weeks of SSRI treatment plus buspirone or placebo.

Results: More patients reported sexual dysfunction in response to direct questioning (41%) as compared with spontaneous report (6%) ($p < .001$). Sexual dysfunction correlated with the duration of the depressive episode, but not with age, dose of SSRI, plasma level of SSRI, duration of SSRI treatment, or any measurement of depression. No statistically significant differences regarding the incidence of sexual dysfunction were found between the citalopram and the paroxetine groups.

Conclusion: Open-ended questions are an insufficient tool to estimate sexual dysfunction, and premarketing clinical trials should therefore include basic explicit assessments. The failure to find a correlation between treatment duration and sexual dysfunction adds to the notion that sexual side effects due to SSRIs do not abate over time.

(J Clin Psychiatry 2005;66:100–106)

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The clinical trial in which data for this study were collected was sponsored by Bristol-Myers Squibb, Sweden. The lead author is supported by the Swedish Research Council for Medicine (grant no. 529-2002-6696), the Swedish Society for Medical Research, and the Göteborg Medical Society.

Mr. Högberg is an employee of Bristol-Myers Squibb. Dr. Thase has been a consultant for AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Novartis, Organon, Pfizer, and Wyeth and has participated in speakers bureaus for AstraZeneca, Eli Lilly, GlaxoSmithKline, Organon, and Wyeth.

The authors thank Kerstin Torstensson for help with data management and Christine Johnson for help with preparing the manuscript.

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Sexual side effects are common and unwelcome side effects of treatment with many psychotropic drugs and have for good reasons been the focus of a number of recent reviews.[1–7] Provided that the patient perceives the causal connection between sexual dysfunction and the drug, sexual dysfunction might be a reason for nonadherence to medication that ultimately results in treatment failure.[8–10] If, on the other hand, the relationship between the drug and the sexual dysfunction remains undiscovered, or if the patient continues to take the medication despite the sexual side effects, the end result could be a markedly decreased quality of life.[11,12] Either way, it is of significant clinical importance for both clinical investigators and clinicians to find the best way to gain reliable information about whether patients experience sexual side effects.

In clinical trials, "treatment-emergent side effects," i.e., adverse events that occur for the first time or worsen during therapy following a baseline evaluation, are typically elicited by open-ended questions, for example, "Have you felt different in any way since starting the new treatment/since the last visit?" This way of gaining information about side effects has been preferred because the questions are nonleading and less likely to detect side effects that neither the patient nor the investigator believes

are significant. By using open-ended questions, efficacy trials of the selective serotonin reuptake inhibitors (SSRIs) have detected a relatively low incidence of sexual side effects. In the premarketing program for the SSRI citalopram, as summarized in the *Physicians' Desk Reference*,[13] the rates for decreased desire and anorgasmia in women were 1.3% and 1.1%, respectively; the incidence of decreased desire and abnormal ejaculation in men was 6.1% and 3.8%, respectively. Similarly, in premarketing clinical trials for depression with the SSRI paroxetine, 2% of the women reported anorgasmia, 3% of patients of both sexes reported decreased libido, and 13% of the men reported ejaculatory delay.[13] With the wide use of SSRIs, however, has come a growing recognition that the true incidence of adverse sexual effects is several orders of magnitude higher than these figures suggest.[2,3] It has been assumed that the reason for the discrepancy between the premarketing findings and independent estimates of sexual dysfunction is that open-ended questions are inadequate to elicit complaints of sexual dysfunction. Sexual matters are private in nature, it is reasoned, and therefore both patients and doctors are reluctant to discuss sexual problems in the clinical setting. However, few studies have addressed whether direct questioning is more accurate than spontaneous report in assessing sexual dysfunction.

To the best of our knowledge, no study has investigated the discrepancy between spontaneous report and direct questioning during double-blind treatment with SSRIs. The present study is further unique in its focus on patients who are not responding to SSRIs, i.e., a population in which it is of great importance to weigh beneficial drug effects against potential negative consequences.

The objectives of this study were 3-fold: (1) to investigate the concordance between spontaneously reported and systematically inquired sexual dysfunction; (2) to compare citalopram and paroxetine with regard to their propensity to cause sexual side effects; and (3) to investigate the correlation between sexual dysfunction and illness severity and treatment duration as well as the dose/serum concentration of the SSRIs.

METHOD

A randomized, placebo-controlled trial was conducted to study the efficacy of buspirone augmentation of SSRI therapy in treatment-refractory depression. The results from this trial have previously been described in detail.[14] In conclusion, the study failed to demonstrate any difference in efficacy between buspirone and placebo augmentation of the SSRIs.

Human Subjects

Patients over 18 years of age were enrolled from 12 centers in Sweden and 1 in Norway. All patients met the criteria for a major depressive episode according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV). Patients had not responded to treatment with either citalopram or paroxetine for a minimum of 4 weeks prior to the study (median time treated = 140 days). During the last 2 weeks of therapy, the doses were at least 30 mg of paroxetine (mean dose at baseline = 39.8 mg) or 40 mg of citalopram (mean dose at baseline = 46.1 mg). Nonresponse was defined as a Clinical Global Impressions-Improvement (CGI-I)[15] rating of "worse," "no improvement," or "minimal improvement" during the last 2 weeks of therapy. The exclusion criteria were pregnancy or use of an unreliable contraceptive method, epilepsy, severe somatic disease, mental disorder due to a general medical condition, substance abuse, highly suicidal status, and any other psychiatric disorder except generalized anxiety disorder or specific phobias.

Assessments

Each patient was evaluated before and after 4 weeks of double-blind treatment with placebo (N = 60) or buspirone (N = 59). Antidepressant outcomes were assessed with the Clinical Global Impressions-Severity of Illness scale (CGI-S),[15] the Montgomery-Asberg Depression Rating Scale (MADRS),[16] 4 Visual Analogue Scales (VAS) ("irritability," "mood," "power of initiative," and "interest"), and the Global Assessment of Functioning (GAF)[17] of DSM-IV.

To assess side effects, patients were first asked a nonleading question such as "Have you felt different in any way since you started the new treatment?" Thereafter, patients were asked direct questions with regard to specific side effects using the UKU Side Effect Rating Scale,[18] which has been used previously to assess drug-induced sexual dysfunction.[19–22] The UKU is a structured safety rating scale that explicitly asks about a number of side effect symptoms, rated on a 4-point scale on which 0 = no, 1 = mild, 2 = moderate, and 3 = severe. Three items regarding sexual dysfunction were used in this study: decreased desire, orgasmic dysfunction, and (for men) ejaculatory dysfunction.

Analysis of Serum Drug Concentration

At baseline, blood samples were obtained for the analysis of serum drug levels of citalopram and paroxetine. For analyses of racemic citalopram, its main metabolite desmethylcitalopram, and paroxetine, established high-performance liquid chromatography with ultraviolet detection methods,[23,24] which had been slightly modified for routine therapeutic drug monitoring purposes, were used.

Ethical Considerations

This study was carried out according to the Declaration of Helsinki. The institutional review boards of the respec-

Table 1. Demographic Data Stratified by Sex and Drug Treatment

Variable	Women		Men	
	Citalopram (N = 55)	Paroxetine (N = 27)	Citalopram (N = 22)	Paroxetine (N = 15)
Age, mean (SD), y	46 (12)	48 (14)	47 (16)	47 (11)
Duration of ongoing depressive episode, median (range), d	243 (42–6209)	304 (56–2009)	243 (91–548)	304 (56–1826)
Duration of SSRI treatment, median (range), d	139 (32–818)	162 (44–982)	138 (29–565)	155 (28–513)
Dose of SSRI in the last 2 weeks, mean (SD), mg/d	45 (8.6)	40 (9.4)	49 (11.5)	39 (9.9)
CGI-S score, mean (range)	4.6 (3–6)	4.6 (3–6)	4.5 (3–6)	4.6 (4–6)
MADRS score, mean (range)	28 (14–42)	28 (14–40)	25 (12–40)	29 (16–48)
GAF score, mean (SD)	50 (9.8)	52 (9.1)	52 (8.9)	50 (10.7)

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

Table 2. Correlation of Decreased Libido (rated 0–3) and Orgasm Dysfunction (rated 0–3) in Men Treated With Citalopram or Paroxetine[a]

Orgasm Dysfunction Rating	Decreased Sexual Desire Rating			
	0	1	2	3
0	17	5	1	2
1	2	0	2	0
2	2	0	5	0
3	0	0	0	1

[a]Data shown are Ns.

Table 3. Correlation of Decreased Libido (rated 0–3) and Orgasm Dysfunction (rated 0–3) in Women Treated With Citalopram or Paroxetine[a]

Orgasm Dysfunction Rating	Decreased Sexual Desire Rating			
	0	1	2	3
0	53	3	4	3
1	1	4	1	0
2	1	0	6	1
3	1	0	0	4

[a]Data shown are Ns.

tive sites approved the study protocol. All patients consented orally and in writing to participate in the study.

Statistics

The Pearson χ^2 test was employed to test for statistical significance of the relationship between categorical variables; when cells comprised ≤ 5 cases, the Yates correction for small samples was applied. The McNemar χ^2 was used for within-subjects 2-by-2 tables. For correlations, the Pearson product moment correlation was used. For group comparisons of the sexual dysfunction score (see Results), the nonparametric Mann-Whitney U test was used. To assess the agreement between the baseline side effect rating and the side effect rating after 4 weeks, the Cohen kappa coefficient was calculated. For all tests, alpha was set at $p \leq .05$.

RESULTS

Demographic Data

Patients' demographic characteristics and measurements of depression, stratified by sex and drug, are displayed in Table 1. The total cohort comprised 119 subjects, 82 women and 37 men. The mean (SD) age in the total group was 46 (13) years. Subjects' median CGI-S score was 5 (range, 3–6), their median MADRS score was 28 (range, 12–48), and their median GAF score was 51 (range, 30–75). Seventy-seven patients had received citalopram for a median (range) of 141 (29–818) days; the mean (SD) dose during the last 2 weeks was 46 (9.6) mg/day. Forty-two patients had received paroxetine treatment for a median (range) of 149 (28–982) days; the mean (SD) dose during the last 2 weeks was 40 (9.5) mg/day.

Relationship Between Ejaculatory Dysfunction, Orgasm Dysfunction, and Decreased Desire

There was an almost complete overlap between ejaculatory and orgasmic dysfunction in men ($r = 0.90$, $p < .001$); all patients who reported ejaculatory dysfunction also reported orgasmic dysfunction. Therefore, these 2 items were merged in men and the highest rating of these 2 items was translated into the orgasmic dysfunction item. Although decreased desire correlated with orgasmic dysfunction in both men ($N = 37$, $r = 0.47$, $p = .003$) and women ($N = 82$, $r = 0.63$, $p < .001$), many individuals experienced decreased desire without orgasm dysfunction and vice versa (Tables 2 and 3). We therefore added these ratings to obtain a "sexual dysfunction score" (rated 0–6).

Open-Ended Versus Direct Questioning

In response to the open-ended question, 7 patients (6%) reported any sexual side effect, as compared with 49 patients (41%) who endorsed any sexual side effect in response to direct questioning. This large difference (odds ratio = 11, 95% CI = 5 to 26) was statistically significant ($\chi^2 = 45$, $p < .001$). Comparing the sexes revealed that 2 women (2%) and 5 men (14%) reported sexual side effects in response to the open-ended question ($\chi^2 = 6.7$, $p = .01$, Yates corrected χ^2 test), while 29 women (35%) and 20 men (54%) did so in response to the direct questioning ($\chi^2 = 3.7$, $p = .06$). Specifically, decreased desire

Table 4. Frequency of Sexual Side Effects in Response to Open-Ended and Direct Questioning in Patients With Treatment-Refractory Depression: Comparison Between Citalopram and Paroxetine

	Women			Men			Women and Men		
Assessment	Citalopram (N = 55)	Paroxetine (N = 27)	p	Citalopram (N = 22)	Paroxetine (N = 15)	p	Citalopram (N = 77)	Paroxetine (N = 42)	p
Open-ended question, any sexual side effect, N (%)	1 (2)	1 (4)	.81[a,b]	3 (14)	2 (13)	.64[a,b]	4 (5)	3 (7)	.98[a,b]
Direct questioning, any sexual side effect, N (%)	21 (38)	8 (30)	.45[a]	13 (59)	7 (47)	.46[a]	34 (44)	15 (36)	.37[a]
Decreased desire, N (%)	19 (35)	7 (26)	.32[a]	12 (55)	4 (27)	.18[a,b]	31 (40)	11 (26)	.12[a]
Orgasmic dysfunction, N (%)	16 (29)	3 (11)	.12[a,b]	7 (32)	5 (33)	.79[a,b]	23 (30)	8 (19)	.20[a]
Sexual dysfunction score (0–6), mean	1.30	0.70	.29[c]	1.64	1.00	.33[c]	1.40	0.81	.18[c]

[a]χ^2 test, citalopram versus paroxetine.
[b]Yates correction for small samples.
[c]Mann-Whitney U test.

was reported by 16 men (43%) and 26 women (32%); orgasmic dysfunction was reported by 19 women (23%) and 12 men (32%). The patients' report of sexual side effects stratified by sex and antidepressant drug is shown in Table 4.

Citalopram Versus Paroxetine

Few patients reported any sexual side effect on the open-ended question (citalopram, N = 4 [5%]; paroxetine, N = 3 [7%]). On direct questioning, 34 (44%) of the patients treated with citalopram and 15 (36%) of those treated with paroxetine reported any sexual side effect; this difference was not statistically significant ($\chi^2 = 0.80$, p = .37). As shown in Table 4, there were no statistically significant differences between the 2 SSRIs with regard to sexual side effects.

Correlations

The sexual dysfunction score correlated weakly with the duration of the current depressive episode (r = 0.19, p = .043), but not with patients' age (r = 0.00, p = .98), dose of citalopram (r = 0.16, p = .18) or paroxetine (r = 0.14, p = .39), plasma level of citalopram (r = 0.04, N = 75, p = .72) or paroxetine (r = 0.22, N = 42, p = .16), duration of SSRI treatment (r = 0.10, p = .26), CGI-S score (r = –0.09, p = .98), MADRS score (r = –0.13, p = .14), or GAF score (r = 0.13, p = .15).

Group Comparisons

Patients who experienced any sexual side effect did not differ from the group that did not experience sexual side effects with respect to duration of the depressive episode and SSRI treatment, dose and serum concentration of SSRI, age, or CGI-S, MADRS, or GAF score (data not shown).

Repeated Assessment

A confounder in this study is that the participants' depression at baseline might in itself contribute to sexual dysfunction. One way to sort out the relative importance of depression and drug treatment for the reported sexual side effects is therefore to investigate if subjects who were no longer depressed after 4 weeks of SSRI plus placebo treatment differed regarding sexual side effects at endpoint from those treated with SSRI plus placebo who remained depressed. To this end, the group that received SSRI plus placebo (N = 60) was stratified into responders (N = 28) and nonresponders (N = 32) with respect to depression. In the responding group, 9 subjects (32%) reported sexual dysfunction at baseline compared with 5 subjects (18%) after 4 weeks of treatment. In the nonresponse group, 11 subjects (34%) reported sexual side effects at baseline compared with 9 subjects (28%) after 4 weeks of treatment. These changes in sexual dysfunction during SSRI plus placebo treatment were not statistically significant in the response group ($\chi^2 = 0.64$, p = .42, McNemar χ^2) or in the nonresponse group ($\chi^2 = 0.05$, p = .82, McNemar χ^2), nor did the relative change in sexual dysfunction across the study differ between the response group (in which sexual dysfunction remitted in 4 of 28 patients) and the nonresponse group (in which sexual dysfunction remitted in 2 of 32 patients) ($\chi^2 = 0.26$, p = .61, Yates corrected χ^2 test).

Test-Retest Reliability

The degree of agreement between the baseline rating of sexual side effects and the rating after 4 weeks of treatment with SSRI plus placebo was investigated. Whereas 14 subjects reported sexual dysfunction at both baseline and endpoint, 38 subjects reported no sexual dysfunction at either baseline or endpoint. Two subjects reported sexual dysfunction at baseline but not endpoint, while 6 reported sexual dysfunction at endpoint but not baseline. This yields an observed Cohen κ coefficient of 0.68 (N = 60, $p < .001$). However, the maximum possible value of κ is 0.84 (not 1.0) because there are different numbers of subjects in the 4 categories. The observed κ should therefore be corrected by dividing by the maximum possible value (0.68/0.84). The resulting ratio, 0.81, represents excellent "test-retest" agreement.[25]

DISCUSSION

This study assessed sexual dysfunction, by means of both open-ended questions and direct questioning, in patients with refractory depression who had been treated with either citalopram or paroxetine for at least 1 month. The ratio of citalopram- to paroxetine-treated patients was in due proportion to the use of the respective drugs in Sweden at the time data were collected.

The first finding was that decreased desire and orgasm dysfunction were only partly overlapping. This suggests that these symptoms should be assessed separately. By contrast, the assessment of ejaculatory dysfunction and orgasm dysfunction in men did not yield more information than the assessment of ejaculatory dysfunction alone; these 2 items can therefore be collapsed into one.

The second finding was that more men than women reported sexual dysfunction in response to both open-ended ($p = .01$) and direct ($p = .06$) questioning, which confirms the findings of several previous studies.[19,26,27] The fact that the opposite sex ratio is found in the general population—in which more women than men report sexual dysfunction[28]—suggests that this is a true sex difference in pharmacodynamic response to SSRIs rather than a sex difference in terms of readiness to report these symptoms.

The third finding was that the incidence of sexual dysfunction was much higher when direct questioning was used compared with when open-ended questioning was used (odds ratio = 11.2). This finding mirrors a previous study of 344 patients receiving treatment with SSRIs for various diagnoses in which explicit interview yielded a 4 times higher incidence of sexual dysfunction (58%) than spontaneous report (14%).[29] A large-scale study comprising 4557 depressed patients that used various SSRIs found a surprisingly high incidence of spontaneously reported problems (35%), but still, the incidence doubled with direct questioning (69%).[30] Together, these studies provide strong empirical support for the notion that spontaneous report underestimates the incidence of sexual dysfunction and that therefore an explicit interview is required in order to obtain reliable estimates.

Given that sexual dysfunction affects adherence and quality of life, accurate measures of sexual dysfunction are warranted in phase 3 trials of new psychotropic drugs. It might, however, be argued that direct questioning about sexual dysfunction would distort the response to the open-ended questions that are important to detect unexpected side effects. This dilemma could, however, be circumvented by conducting the detailed interview after the open-ended question at the last visit of the trial. With respect to drugs already on the market, it would be both labor-intensive and financially prohibitive to perform additional clinical trials for the sole purpose of assessing sexual effects. Data about sexual dysfunction must therefore be obtained through more cost-effective surrogate measures. One method that is believed to yield reliable and clinically valid measures of drugs' propensity to cause sexual dysfunction is the assessment of drug effect on ejaculation latency in healthy young men.[11,31] This method requires much fewer resources than conventional clinical trials for depression and might therefore be a cost-effective way to evaluate drugs.

In the clinical setting, time is always an issue, and privately completed questionnaires therefore seem like an attractive option. One study of sexual side effects due to an antihypertensive medication found that 47% of patients reported sexual side effects after privately completing a questionnaire, which represents an increase from 26% of patients who reported sexual side effects after a systematic interview, and only 10% who reported them spontaneously, suggesting that self-report questionnaires are sensitive instruments.[32] Less encouraging, however, is an investigation of sexual dysfunction due to a tricyclic antidepressant drug which concluded that questionnaires were no better than spontaneous reports in eliciting reports of sexual dysfunction.[33]

The failure in the present study to demonstrate a relationship between sexual dysfunction and plasma concentration of SSRI should come as no surprise. Previous studies have demonstrated that monitoring the plasma concentration of SSRIs has no predictive value for therapeutic effect or side effects.[34] As has been discussed earlier,[35] there may be several reasons for this lack of correlation between serum concentration and side effects and therapeutic effects, such as individual differences in the plasma/cerebrospinal fluid concentration ratio,[36] individual differences in the ratio of parent drug and metabolites in plasma, and that virtually all patients have drug concentrations high enough to cause the effect in question.

When an SSRI is taken chronically, most side effects subside during the course of treatment. Whether this is also true for sexual dysfunction is a contentious issue; whereas some studies suggest that sexual dysfunction abates as a function of time,[37] other studies suggest that no tolerance develops.[29,33,38] In this study, we found a 10% reduction in the frequency of sexual dysfunction across 4 weeks of therapy—dysfunction at baseline was highly correlated with dysfunction at endpoint. Moreover, we did not find the negative correlation between the duration of SSRI treatment and sexual dysfunction that would have been expected if tolerance had developed. This study therefore lends further support to the notion that sexual side effects due to treatment with SSRIs do not subside over time.

Three open studies have explicitly assessed sexual dysfunction with both citalopram and paroxetine (along with other antidepressants). The first study, comprising 235 patients, found a higher incidence of sexual dysfunc-

tion with paroxetine (75.5%) than citalopram (28.9%),[39] whereas the second study with over 1000 patients found a similar incidence of sexual dysfunction with paroxetine (70.7%) and citalopram (72.7%).[26] In the third study, paroxetine had a higher rate of sexual dysfunction than citalopram, but the difference was not statistically significant.[3] One head-to-head, double-blind study evaluated the effect of paroxetine 20 mg and citalopram 20 mg on the delay in time to ejaculation in men with premature ejaculation—which is considered a surrogate measure of sexual side effects—and found that paroxetine caused a considerably greater delay than citalopram.[40] In the present study, paroxetine and citalopram did not differ significantly regarding the incidence of sexual dysfunction, although both men and women treated with citalopram had a numerically greater incidence of sexual dysfunction than subjects treated with paroxetine. This finding might, however, be explained by selection bias since patients were not randomly assigned to citalopram or paroxetine. In other words, patients with preexisting sexual dysfunction might more often have been prescribed citalopram, a phenomenon that has been discussed previously.[3]

Some facets of this study need to be considered. First, there are scales other than the UKU available to assess drug-induced sexual dysfunction.[41,42] Although the UKU items have not been validated against any of these scales, it is conceivable that the UKU items for sexual dysfunction are less sensitive, which could yield apparently lower rates of sexual dysfunction in this study compared with studies using more elaborate scales to assess sexual satisfaction. Second, patients had been taking either citalopram or paroxetine for a minimum of 4 weeks without responding before entering this study. Hence, the patients knew which drug (citalopram or paroxetine) they were taking, which implies a risk of overestimating the incidence of sexual dysfunction. On the other hand, this effect might have been counteracted by the fact that the focus in this trial was on depressive symptoms rather than sexual side effects. Third, sexual dysfunction is a frequent symptom per se in depression.[19,30,43–47] Therefore, the present study's baseline measure of sexual dysfunction might reflect the symptomatology of refractory depression or premorbid sexual dysfunction rather than an actual drug effect. This is, however, unlikely given that no statistically significant difference in sexual dysfunction was found between the placebo-treated subjects whose depression did and did not improve. In addition, although a weak positive correlation between sexual dysfunction and the duration of the depressive episode was discernible, there was no relationship between the measures of depression severity and sexual dysfunction. Finally, the group with sexual dysfunction did not differ on any measure of depression from the group without sexual dysfunction. In sum, these findings make it conceivable that the sexual dysfunction seen in this study for the most part can be attributed to drug treatment.

Drug names: buspirone (BuSpar and others), citalopram (Celexa), paroxetine (Paxil and others).

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