Assessing the Onset of Antidepressant-Induced Sexual Dysfunction Using Interactive Voice Response Technology

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Background: Sexual dysfunction is a symptom of major depression, as well as a common complication of treatment with many classes of antidepressants. Nonetheless, the various forms of sexual dysfunction continue to be underreported in clinical practice, despite the availability of validated scales such as the Changes in Sexual Functioning Questionnaire (CSFQ). The current study was designed to evaluate the validity of obtaining CSFQ data using interactive voice response (IVR) technology.

Method: Sexually active, healthy male volunteers (N = 99; mean age of 31 years) were randomly assigned to 3 weeks of double-blind, parallel-group treatment with paroxetine (20 mg/day); CP-448,187 (3 mg/day); or placebo. Patients completed both paper-and-pencil and IVR versions of the 14-item CSFQ at baseline and on treatment days 8, 15, and 21. Additional IVR assessments were obtained at days 2, 4, and 6, permitting assessment of changes between office visits. This study was conducted between March and May 2001.

Results: The overall correlation between the paper and IVR CSFQ total score was r = 0.96 ($p < .0001$). Similarly, high correlations were found between paper and IVR assessment methods on the individual CSFQ subscales: pleasure (r = 0.88), frequency (r = 0.88), interest (r = 0.93), arousal (r = 0.89), and orgasm (r = 0.92; $p < .0001$ for all comparisons). Both assessment methods were able to detect a statistically significant between-group difference in sexual functioning by day 8, which remained significant throughout the remainder of the study. Both assessment methods found SSRI-related sexual dysfunction to include significant effects on all CSFQ domains. Assessments using IVR collected from subjects at home on days 2, 4, and 6 identified onset of sexual dysfunction by day 4, before it was detected during scheduled office visits.

Conclusion: Interactive voice response assessment of sexual dysfunction on the CSFQ was found to be highly correlated with previously validated paper-and-pencil assessment. Interactive voice response provides a valid, easy-to-administer alternative method for obtaining systematic data on the impact of antidepressant treatment on sexual functioning. More frequent assessment by IVR enables more precise evaluation of symptom onset.

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Treatment-emergent sexual dysfunction is a well-recognized adverse effect associated with the administration of most currently marketed antidepressants. Tricyclic antidepressants, monoamine oxidase inhibitors,[1] selective serotonin reuptake inhibitors (SSRIs),[2,3] and newer medications such as serotonin-norepinephrine reuptake inhibitors[4] have all been linked to impairments in each phase of the sexual response cycle (interest, arousal, and orgasm) and to effects on sexual frequency and pleasure. These events not only affect patient quality of life, but also impact disease management by contributing to patient nonadherence and physician prescribing practices (e.g., underdosing, switching, and pharmacologic augmentation).[5,6]

Although impairment of sexual function has become a primary concern of physicians prescribing antidepressants as well as of patients receiving them, numerous obstacles limit current understanding of this issue. Among these is the historical underreporting of sexual dysfunction. Physicians have underestimated the prevalence of sexual dysfunction by failing to solicit specific informa-

tion from patients. It has been shown repeatedly that sensitive topics such as sexual functioning are more readily disclosed by subjects in computer interviews than in human interviews.[7–10] Retrospective recall ability, discomfort with the topic, lack of knowledge, and reluctance to volunteer such information have contributed to patient underreporting.[11,12] In addition, several psychiatric conditions, including depression, have been associated with comorbid sexual dysfunction prior to the initiation of pharmacotherapy.[5,13] These preexisting disorders may confound the ability to detect change and assign causality.

To date, only a few well-controlled, prospective studies have examined issues relating to antidepressant-induced sexual dysfunction.[1,2,4] Therefore, limited information is currently available regarding the timing or chronology of sexual side effects attributable to pharmacologic intervention. This study was designed to examine the time course of SSRI-related sexual dysfunction by serial completion of the Changes in Sexual Functioning Questionnaire (CSFQ)[14–16] and to compare the results of the traditionally administered CSFQ with results obtained when the scale is completed via interactive voice response (IVR) technology. Since the sexual dysfunction associated with SSRIs is a class effect,[17] paroxetine in a daily dose of 20 mg was selected as a representative SSRI antidepressant. CP-448,187, an experimental antidepressant with a high affinity for the 5-HT_{1B} receptors, was used as the second treatment group in a daily dose of 3 mg, and a parallel placebo comparator was used to permit SSRI-specific sexual effects to be discriminated from nonspecific (illness-related) effects. The sensitivity of the CSFQ for detecting treatment-emergent sexual dysfunction was compared using the traditionally administered (paper-and-pencil) version of the CSFQ and the same version of the CSFQ administered via IVR technology. Interactive voice response methodology allows less intrusive and more frequent sampling of the population, reducing retrospective recall problems inherent in more widely spaced assessments, and may enable more precise evaluation of symptom onset.

METHOD

Subjects

The study was performed in healthy males in order to remove any potentially confounding factors associated with depressive illness or hormonal cycling. A total of 99 sexually active, heterosexual males (aged 19–45 years; mean age ranging from 29.0 to 32.2 years among the treatment groups; 69% white) were recruited by means of print advertisements. Inclusion criteria required subjects to be in good health, free of prescription and over-the-counter drugs (except for aspirin, ibuprofen, or acetaminophen), and sexually active at least 2 times per week with a steady partner for the 3 months prior to study entry. Subjects were excluded if they had a history of any of the following: sexual dysfunction, surgical or medical procedure on reproductive/genitourinary organs, positive HIV status, or any known sexually transmittable disease. Also excluded were subjects with a clinically significant and currently relevant medical history, history of depression or any psychiatric illness, drug or alcohol dependence, and habitual tobacco or other nicotine usage.

Study Design

This was a parallel-group, multicenter, randomized, double-blind, placebo-controlled, outpatient study of the effect of an SSRI antidepressant (paroxetine) versus a non-SSRI antidepressant with 5-HT_{1B}–antagonist activity (CP-448,187) versus placebo on sexual function in sexually active, healthy, heterosexual men.

This study was conducted between March and May 2001 in compliance with Institutional Review Board/Independent Ethics Committee (IRB/IEC) informed consent regulations and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines. Before initiating the trial, the investigators/institutions obtained written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, a written informed consent form, subject recruitment procedures (e.g., advertisements), and written information to be provided to subjects. All subjects provided written informed consent.

At screening, informed consent was obtained and medical history, physical examination, electrocardiogram (ECG), and laboratory safety tests, including urine drug screen, were performed. The time between the screening visit and study day 0 was 14 days. Subjects who met entry criteria were randomly assigned to 1 of 3 treatment groups (placebo, 20 mg q.d. of paroxetine, or 3 mg q.d. of CP-448,187) on day 0 of the study.

Baseline safety, sexual function, and adverse event assessments were performed on day 0. During this visit, subjects first completed the paper-and-pencil CSFQ. Other assessments were performed; then, subjects were instructed in the use of the IVR CSFQ administration, and they completed the questionnaire via telephone. The duration of drug treatment was 3 weeks or 21 days and began the day after day 0 (day 1). During treatment, subjects took 2 tablets daily (double dummy) and were encouraged to maintain their usual sexual behavior. Once dosing began, the subjects returned to the clinical research facility weekly on days 8, 15, and 21 to report adverse events, to have pharmacokinetic and safety samples collected, to complete the sexual function assessment (CSFQ, paper version), and to have their outpatient drug inventoried and redispensed.

In addition to the written CSFQ, subjects completed a CSFQ on days 0, 2, 4, 6, 8, 15, and 21 using an IVR

Table 1. Change From Baseline in CSFQ Total and Domain Scores: Day 21 LOCF-Endpoint Analysis of the Paper CSFQ Forms

Measure	Baseline Score, Mean	Change at LOCF Endpoint, Least Squares Mean (SE)	Difference From Placebo, Mean (95% CI)	p Value Versus Placebo
Total CSFQ score				
CP-448,187 (3 mg)	50.3	–1.1 (1.1)	–2.6 (–5.6 to 0.4)	.092
Paroxetine (20 mg)	51.5	–8.7 (8.7)	–13.1 (–13.1 to –7.2)	< .0001
Placebo	52.2	1.1 (1.1)		
CSFQ pleasure				
CP-448,187 (3 mg)	4.0	–0.0 (0.1)	–0.13 (–0.52 to 0.26)	.517
Paroxetine (20 mg)	4.0	–0.8 (0.1)	–0.92 (–1.13 to –0.5)	< .0001
Placebo	4.1	–0.1 (0.1)		
CSFQ desire and frequency				
CP-448,187 (3 mg)	8.1	–0.3 (0.2)	–0.5 (–1.0 to 0.01)	.056
Paroxetine (20 mg)	8.3	–0.9 (0.2)	–1.1 (–1.6 to –0.6)	.0009
Placebo	8.2	0.2 (0.2)		
CSFQ desire and interest				
CP-448,187 (3 mg)	10.7	–0.1 (0.3)	–0.4 (–1.2 to 0.5)	.387
Paroxetine (20 mg)	11.2	–1.2 (0.3)	–1.4 (–2.3 to –0.6)	< .0001
Placebo	11.5	0.3 (0.3)		
CSFQ arousal and erection				
CP-448,187 (3 mg)	12.7	–0.0 (0.4)	–0.6 (–1.6 to 0.4)	.224
Paroxetine (20 mg)	13.2	–1.3 (0.4)	–1.9 (–2.9 to –1.0)	.0002
Placebo	13.3	0.6 (0.4)		
CSFQ orgasm and ejaculation				
CP-448,187 (3 mg)	12.8	–0.5 (0.4)	–1.0 (–2.1 to 0.2)	.097
Paroxetine (20 mg)	12.5	–4.4 (0.4)	–4.8 (–6.0 to –3.7)	< .0001
Placebo	12.8	0.4 (0.4)		

Abbreviations: CSFQ = Changes in Sexual Functioning Questionnaire, LOCF = last observation carried forward.

system. After day 0, subjects were advised to complete the IVR CSFQ in the morning and prior to study visits on days 8, 15, and 21. If subjects had not completed the IVR CSFQ at the time of the study visit, it was completed at the conclusion of the visit.

At the end of drug treatment (day 21 or early termination from the study), the subjects received a physical examination, urinalysis, and ECG and had a blood sample collected for pharmacokinetic and safety laboratory evaluations. Safety samples were obtained again on day 28 (1 week after discontinuation of drug treatment).

Changes in the CSFQ

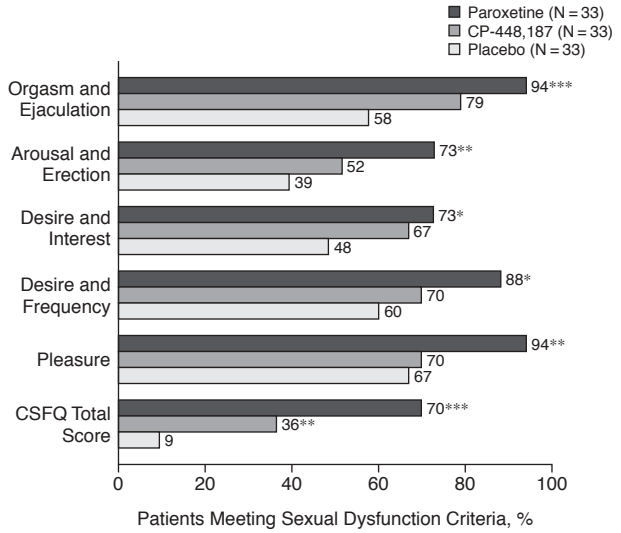
The CSFQ is a structured interview/questionnaire developed specifically to evaluate changes in sexual functioning associated with both psychiatric illness and medication side effects. It has not been validated as an instrument to make a DSM-IV diagnosis of a sexual disorder. The tool was designed to be easy to administer and to be perceived as nonintrusive by test subjects. Both clinical-interview and paper-and-pencil self-report versions are available. The self-report version consists of separate male (used in this study) and female questionnaires. The 14-item, clinical version for males provides a total score as well as subscale scores, which measure activity in 5 domains: interest, frequency, arousal, orgasm, and pleasure. Validation studies have demonstrated that the scale possesses good psychometric properties,[14–16,18] and it has been used in numerous studies evaluating sexual side effects associated with antidepressant treatment.[12,17] Threshold cutoff scores to indicate sexual dysfunction were established in clinical and nonclinical populations by nonoverlap of the 95% confidence interval around the mean for affected populations versus normal controls.[15]

IVR Technology

Interactive voice response technology is a computer-automated touch-tone telephone system used to collect self-report data. Over the past decade, a number of clinical assessment scales have been adapted to IVR. The convenience of remote data capture has allowed more frequent assessments with excellent compliance. A number of studies indicate that personally sensitive information (sexual behavior, drug use) may be more accurately reported in computer interviews.[7–10] This study represented the first attempt at administering the CSFQ via IVR.

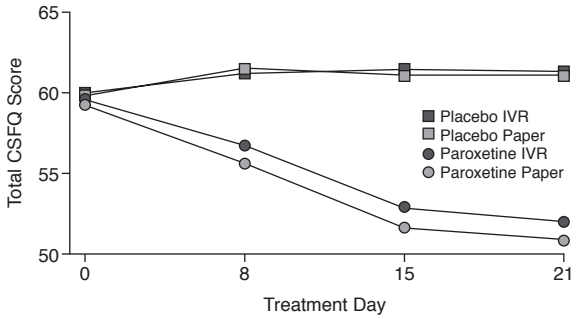
Subjects accessed the IVR system by dialing a toll-free number from a touch-tone telephone and entering an assigned identification number and a 4-digit password of their choosing. The CSFQ questions were read to the subjects by the computer using prerecorded voice files. Following each question, the list of response options was also read. Subjects answered each question by pressing a number on their telephone keypad corresponding to their answer choice. A paper copy of the questionnaire was provided to the subject for reference. Subjects could pause or back up to the previous question by pressing the star key. If no answer was given, the IVR system automatically repeated the question.

Figure 1. The Proportion of Patients at Day 21 Meeting Criteria for Sexual Dysfunction Based on Normative Community Criteria: Results for the Paper Form of the CSFQ Total and Domain Scores



*p < .05.
**p < .01.
***p < .001.
Abbreviation: CSFQ = Changes in Sexual Functioning Questionnaire.

Figure 2. Total CSFQ Scores: Interactive Voice Response (IVR) Versus Paper Administration[a]



[a]Methods of CSFQ administration were statistically equivalent at all timepoints.
Abbreviation: CSFQ = Changes in Sexual Functioning Questionnaire.

Statistical Analysis

Comparisons between the IVR and paper-and-pencil versions of the CSFQ were computed using paired t tests based on the combined analysis sample. Between-treatment group comparisons were primarily made for paroxetine and placebo, since development of the CP-448,187 compound was discontinued. On the primary a priori outcome, change in the CSFQ score at day 21 last-observation-carried-forward (LOCF) endpoint, the analysis was performed for all 3 treatment groups, including CP-448,187. Between-group differences on the change from baseline were computed using univariate analysis of variance. To control for baseline and site differences, the model included main effects for treatment, site, and baseline.

RESULTS

Compliance

The mean length of each IVR call was 3.27 minutes, and the overall compliance rate was 94%. Three percent of the 6% noncompliance rate was attributable to computer system unavailability. There was no significant difference in demographic characteristics, compliance, or discontinuation rates between the treatment groups.

Primary Outcome: Change From Baseline on the CSFQ at Day 21 Endpoint

The mean total CSFQ scores at pretreatment baseline were similar for patients randomly assigned to each of the 3 study treatments. At day 21, treatment with paroxetine was associated with significantly greater impairment in sexual functioning compared with placebo on an LOCF-endpoint analysis of the CSFQ total score (Table 1). A similar significant level of impairment was observed on each of the CSFQ subscale scores, with the greatest treatment effect observed on the orgasm and ejaculation factor (Table 1). Treatment with CP-448,187 was associated with modest but nonsignificant differences from placebo.

The proportion of patients meeting threshold criteria for sexual dysfunction was calculated for the CSFQ total and domain scores, using previously reported normative data.[10] As can be seen in Figure 1, treatment with both paroxetine and CP-448,187 was associated with significantly higher rates of sexual dysfunction using the CSFQ total score threshold criterion. For the individual CSFQ subscale scores, the proportion of patients meeting threshold criteria for sexual dysfunction was elevated on placebo, with rates ranging from 39% to 67%. Treatment with paroxetine was associated with significantly higher rates of sexual dysfunction than placebo on all 5 individual CSFQ domains (Figure 1). Scores for subjects treated with CP-448,187 were higher than placebo, but none of the differences achieved significance.

Paper Versus IVR Administration of the CSFQ

A high degree of correspondence was observed when comparing paper versus IVR administration of the CSFQ on days 0, 8, 15, and 21 (Figure 2).

The overall correlation between the paper and IVR CSFQ total score was $r = 0.96$ ($p < .0001$). Similarly, high correlations were found between paper and IVR assessment methods on the individual CSFQ subscales: pleasure ($r = 0.88$), frequency ($r = 0.88$), interest ($r = 0.93$), arousal ($r = 0.89$), and orgasm ($r = 0.92$, $p < .0001$ for all comparisons).

Table 2. CSFQ Scores By Visit: Comparison of Paper Versus Interactive Voice Response (analysis of combined treatment groups)

Variable	Paper Score, Mean (SE)	Interactive Voice Response Score, Mean (SE)	Difference, Mean (SE)	t	p	r	p for r
Baseline							
Arousal	13.08 (1.58)	13.26 (1.54)	–0.18 (0.87)	–2.045	.044	0.839	< .0001
Pleasure	4.05 (0.64)	4.05 (0.75)	0.00 (0.43)	0.000	1.000	0.820	< .0001
Frequency	8.20 (1.10)	8.14 (1.23)	–0.06 (0.73)	–0.831	.408	0.811	< .0001
Interest	11.15 (1.89)	11.30 (1.81)	0.15 (0.80)	1.884	.062	0.907	< .0001
Orgasm	12.72 (1.43)	12.68 (1.55)	0.04 (0.79)	0.506	.614	0.861	< .0001
Total	59.06 (4.87)	59.30 (5.19)	0.24 (2.16)	1.118	.266	0.910	< .0001
Day 8							
Arousal	13.22 (1.70)	13.27 (1.55)	–0.05 (1.02)	–0.445	.658	0.807	< .0001
Pleasure	3.86 (0.83)	3.88 (0.81)	–0.02 (0.43)	–0.532	.596	0.866	< .0001
Frequency	7.97 (1.22)	8.04 (1.27)	0.06 (0.59)	0.962	.339	0.889	< .0001
Interest	11.09 (2.15)	11.27 (1.96)	0.18 (0.88)	1.803	.075	0.913	< .0001
Orgasm	11.91 (2.31)	12.03 (2.33)	–0.12 (0.99)	–1.026	.308	0.909	< .0001
Total	58.05 (6.07)	58.44 (5.89)	0.38 (1.88)	1.806	.075	0.951	< .0001
Day 15							
Arousal	12.99 (1.98)	13.07 (2.14)	–0.08 (0.78)	–0.980	.330	0.931	< .0001
Pleasure	3.74 (0.92)	3.75 (0.96)	–0.01 (0.45)	–0.241	.810	0.884	< .0001
Frequency	7.87 (1.29)	7.93 (1.21)	0.05 (0.52)	1.043	.300	0.941	< .0001
Interest	10.89 (2.33)	10.89 (2.33)	0.00 (0.78)	0.000	1.000	0.945	< .0001
Orgasm	11.18 (2.87)	11.63 (3.44)	–0.45 (1.37)	–3.036	.003	0.922	< .0001
Total	56.62 (7.77)	57.23 (7.42)	0.61 (2.01)	2.766	.007	0.966	< .0001
Day 21							
Arousal	12.84 (2.24)	12.95 (2.16)	–0.11 (0.77)	–1.394	.167	0.939	< .0001
Pleasure	3.77 (0.91)	3.77 (0.91)	0.00 (0.37)	0.000	1.000	0.916	< .0001
Frequency	7.86 (1.16)	7.95 (1.23)	0.09 (0.50)	1.725	.088	0.915	< .0001
Interest	10.74 (2.21)	10.82 (2.27)	0.08 (0.80)	0.943	.348	0.938	< .0001
Orgasm	11.24 (3.17)	11.43 (3.06)	–0.18 (0.95)	–1.812	.073	0.954	< .0001
Total	56.43 (7.82)	56.79 (7.60)	0.37 (1.87)	1.830	.071	0.971	< .0001

Abbreviation: CSFQ = Changes in Sexual Functioning Questionnaire.

Table 3. Change From Baseline in Total CSFQ Score: Paroxetine Versus Placebo by Assessment Method

	Assessment Method	
Variable	Paper, Mean (SE) Change	Interactive Voice Response, Mean (SE) Change
Day 8		
Paroxetine	–3.43 (0.81)	–2.96 (0.83)
Placebo	1.36 (0.80)	1.16 (0.92)
Difference	4.79 (1.14)	4.12 (1.24)
p	< .0001	.001
Day 15		
Paroxetine	–7.63 (1.10)	–6.53 (1.12)
Placebo	1.44 (1.16)	1.74 (1.14)
Difference	9.07	8.28 (1.60)
p	< .0001	< .0001
Day 21		
Paroxetine	–8.23 (1.14)	–7.56 (1.12)
Placebo	1.68 (1.14)	1.74 (1.13)
Difference	9.90 (1.61)	9.30 (1.58)
p	< .0001	< .0001

Abbreviation: CSFQ = Changes in Sexual Functioning Questionnaire.

A similar pattern was found when examining change scores. The correlation between paper and IVR change in CSFQ total scores across visits was $r = 0.92$ ($p < .0001$). High correlations were also found between paper and IVR assessment methods on the individual CSFQ subscale change scores: pleasure ($r = 0.77$), frequency ($r = 0.72$), interest ($r = 0.79$), arousal ($r = 0.81$), and orgasm ($r = 0.90$, $p < .0001$ for all comparisons).

An examination of mean score differences between the paper and IVR methods by visit (all treatment groups combined) is presented in Table 2. The mean score differences between the paper and IVR methods on both the total CSFQ score and the CSFQ subscales were small and nonsignificant for almost all comparisons. Taken together, these data support the equivalence of the 2 administration methods for the CSFQ.

Effect of Paroxetine Versus Placebo on Sexual Function

Both paper-based and IVR assessments demonstrated a statistically significant difference in sexual functioning reported by subjects receiving paroxetine and those receiving placebo by day 8 ($p \leq .001$, total CSFQ score, Table 3). The paroxetine group reported a decrease in functioning by day 8, which remained significant throughout the study.

The additional IVR assessments administered between baseline and the first study visit (day 8) indicated that a sustained, significant decrease ($p = .025$) in the total CSFQ score occurred as early as day 4 in the paroxetine group (Table 4 and Figure 3).

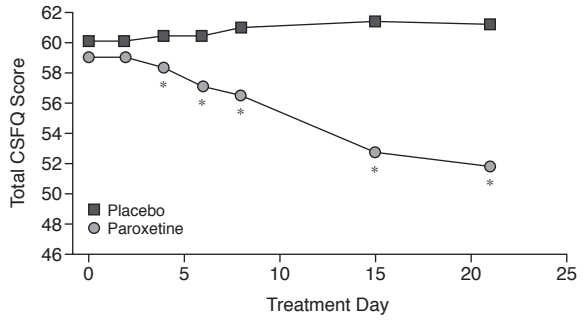
In addition to identifying the onset of sexual dysfunction as measured by the total CSFQ score, the effects on the individual domains of the sexual response cycle (interest, frequency, arousal, orgasm, and pleasure) were

Table 4. Change From Baseline in Total CSFQ Score (interactive voice response administration)

Variable	Interactive Voice Response, Mean (SE) Change
Day 2	
Paroxetine	–0.15 (0.41)
Placebo	0.09 (0.41)
Difference	0.24 (0.58)
p	.675
Day 4[a]	
Paroxetine	–1.70 (0.72)
Placebo	0.91 (0.83)
Difference	2.28 (0.99)
p	.025
Day 6	
Paroxetine	–2.39 (0.79)
Placebo	0.91 (0.83)
Difference	3.30 (1.14)
p	.005

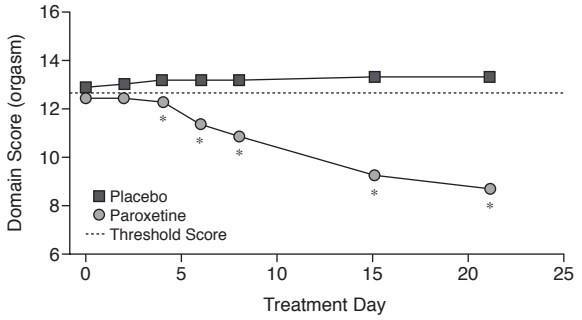
[a]A statistically significant difference between paroxetine and placebo groups occurred by day 4.
Abbreviation: CSFQ = Changes in Sexual Functioning Questionnaire.

Figure 3. Change From Baseline: Total CSFQ Score (interactive voice response administration)



*A statistically significant ($p \leq .05$) decrease in sexual functioning was reported by the paroxetine group by day 4 and was sustained throughout the study.
Abbreviation: CSFQ = Changes in Sexual Functioning Questionnaire.

Figure 4. Change From Baseline: Orgasm Score (interactive voice response administration)[a]



[a]Threshold score was established by nonoverlap of the 95% CI for the mean of affected vs. nonaffected individuals in clinical and nonclinical populations.
*A statistically significant ($p \leq .05$) decrease in the orgasm domain occurred in the paroxetine group by day 4 and was sustained throughout the study.

also examined. Administration of the CSFQ using IVR indicated that administration of the SSRI had significant deleterious effects on the orgasm domain as early as day 4 ($p = .027$, Figure 4 and Table 5) and on the arousal domain by day 6 ($p = .045$, Figure 5 and Table 5).

Interactive voice response assessment indicated that subjects receiving paroxetine experienced significant, sustained decreases in function in all of the remaining sexual function domains (pleasure, frequency, and interest) by day 15 (Table 5).

DISCUSSION

The assessment of medication-induced sexual dysfunction is complicated by several factors. Because patients with depression often experience sexual dysfunction prior to treatment,[13] it has been difficult to differentiate changes in sexual function due to the disease state versus those caused by neurochemical intervention. In order to identify changes in function strictly associated with medication, a healthy population was selected for this study.

The ability to assess dysfunction has been limited by the lack of a systematic approach for obtaining information (i.e., physician inquiry, patient spontaneous self-report). Recently, several instruments have been developed specifically to measure sexual function changes. In this study, the self-report version of the CSFQ was chosen as the data collection tool and was completed weekly by all subjects during office visits. It has been proposed that the personal nature of the information being gathered may affect subject reporting. The use of IVR technology provides a more anonymous environment, which may encourage accurate disclosure by subjects who may be reluctant to share this information in an office setting. While this study established the equivalence of these 2 methods of collecting CSFQ self-report assessments, it was not designed to address differences between face-to-face clinician-collected ratings and self-reported ratings.

This study has examined the validity of administering the CSFQ via IVR and found the datasets collected were statistically equivalent (Figure 2, Tables 2 and 3) at all timepoints, thereby supporting IVR administration of the CSFQ. Repeated administration of the scale, however, was associated with an increased correlation between the administration methods (r values increased as a function of time). This trend was apparent in the CSFQ total score as well as in the domain scores. This increase may be a function of increased familiarity with the instrument (i.e., learning) or may simply be a mathemati-

Table 5. Change From Baseline on CSFQ Subscales (interactive voice response administration)[a]

	Mean (SE) Change From Baseline				
Variable	Pleasure	Frequency	Interest	Arousal	Orgasm
Day 2					
Paroxetine	–0.06 (0.09)	–0.08 (0.13)	–0.12 (0.15)	0.05 (0.17)	–0.03 (0.18)
Placebo	–0.07 (0.09)	–0.08 (0.13)	–0.11 (0.16)	0.22 (0.17)	0.15 (0.18)
Difference	0.00	0.00	0.01	0.17	–0.18
p	.977	.987	.964	.484	.474
Day 4					
Paroxetine	–0.26 (0.13)	–0.39 (0.15)	–0.32 (0.21)	–0.28 (0.26)	–0.52 (0.28)
Placebo	–0.13 (0.13)	–0.06 (0.15)	0.12 (0.21)	0.24 (0.25)	0.36 (0.27)
Difference	0.13	0.33	0.43	0.52	0.88
p	.483	.115	.147	.155	.027*
Day 6					
Paroxetine	–0.26 (0.12)	–0.33 (0.17)	–0.25 (0.24)	–0.43 (0.27)	–1.12 (0.29)
Placebo	0.03 (0.13)	–0.13 (0.18)	0.18 (0.25)	0.36 (0.28)	0.38 (0.31)
Difference	0.29	0.20	0.43	0.80	1.50
p	.096	.424	.217	.045*	.001*
Day 8					
Paroxetine	–0.30 (0.13)	–0.19 (0.18)	–0.36 (0.23)	–0.59 (0.25)	–1.60 (0.35)
Placebo	0.08 (0.15)	0.04 (0.20)	0.27 (0.25)	0.40 (0.27)	0.40 (0.39)
Difference	0.38	0.23	0.63	0.98	2.00
p	.063	.384	.072	.010*	.000*
Day 15					
Paroxetine	–0.74 (0.16)	–0.60 (0.19)	–1.00 (0.33)	–0.98 (0.36)	–3.36 (0.41)
Placebo	0.07 (0.16)	0.25 (0.19)	0.06 (0.34)	0.69 (0.36)	0.63 (0.41)
Difference	0.81	0.85	1.06	1.67	3.98
p	.001*	.002*	.027*	.001*	.000*
Day 21					
Paroxetine	–0.72 (0.14)	–0.75 (0.19)	–1.00 (0.32)	–1.32 (0.35)	–3.91 (0.42)
Placebo	0.17 (0.15)	0.33 (0.20)	0.20 (0.32)	0.70 (0.35)	0.55 (0.43)
Difference	0.89	1.08	1.20	2.02	4.46
p	.000*	.000*	.009*	.000*	.000*

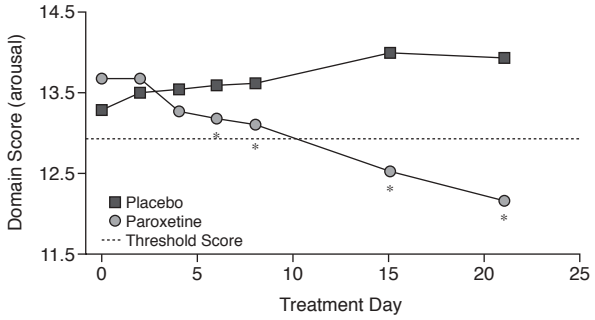
[a]Paroxetine use is associated with deleterious effects in all domains of the sexual response cycle.
*Dysfunction in orgasm and arousal subscales is apparent in less than 1 week, and all domains experience significant decreases in function by 2 weeks.
Abbreviation: CSFQ = Changes in Sexual Functioning Questionnaire.

cal result of the increased range in scores associated with paroxetine use, as increases in range drive increases in correlation.[18] A further limitation of this study includes possible memory effects, as the time between the 2 forms of assessment on days 8, 15, and 21 was not controlled, although different tasks, both in the study and in daily life, between the 2 administrations could have mitigated these effects. Also, IVR ratings obtained on days 2, 4, and 6 outside the office differentiated paroxetine from placebo and should not have been substantially influenced by memory of earlier ratings.

In addition to anonymity, IVR provides a convenient way to remotely collect self-report data. This allows more frequent assessments, which may in turn provide increased precision. Interactive voice response and paper-collected datasets demonstrate that 20 mg of paroxetine q.d. is associated with a significant, deleterious change in the overall level of sexual functioning as measured by the CSFQ total score by day 8 (Figure 2). Additional timepoints collected outside office visits via IVR indicate that this change occurs as early as day 4 and that the level of function continues to decline until week 3 (Table 4 and Figure 3). Although it has been suggested that tolerance may develop, the length of this study was insufficient to observe any reversal in the dysfunction associated with paroxetine use.

The use of SSRIs has been primarily associated with changes in orgasm and arousal, particularly in men.[19] Data from this study indicate that the timing of deleterious effects on the orgasm and arousal domains are closely linked to the onset of overall sexual dysfunction (CSFQ total score). Significant changes in the orgasm domain resulting from 20 mg of paroxetine occur as early as day 4 (Figure 4), while changes in arousal become statistically significant by day 6 (Figure 5). The chronology of sexual dysfunction occurring in the orgasm and arousal domains may help to explain why these events are strongly associated with SSRI use. Data collected in this study, however, demonstrate that paroxetine use continues to affect all aspects of the sexual response cycle. By day 15, the domains of pleasure, frequency, and interest are all significantly affected (Table 5). Dysfunction in these domains may receive less attention due to the fact that the overall diagnosis of sexual dysfunction can be made based on changes in orgasm and arousal, which occur several weeks before any changes in pleasure, frequency, or interest occur.

Figure 5. Change From Baseline: Arousal Score (interactive voice response administration)[a]



[a]Threshold score was established by nonoverlap of the 95% CI for the mean of affected vs. nonaffected individuals in clinical and nonclinical populations.
*A statistically significant ($p \leq .05$) difference between paroxetine and placebo groups occurred in the arousal domain by day 6 and was sustained throughout the study.

This study represents an initial attempt to examine the chronology associated with antidepressant-induced sexual dysfunction and to understand those effects that may be directly attributable to medication use in the absence of an underlying psychiatric disorder. Additional prospective well-controlled studies will need to be performed in populations of interest using a number of antidepressant agents. Interactive voice response assessment, through its inherent anonymity and potential for increased assessment frequency, may be especially well suited for collecting data on sexual functioning.

Drug name: paroxetine (Paxil and others).

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