ORIGINAL RESEARCH

Effect of Vortioxetine vs. Escitalopram on Sexual Functioning in Adults with Well-Treated Major Depressive Disorder Experiencing SSRI-Induced Sexual Dysfunction

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ABSTRACT

Introduction. Sexual dysfunction is common with serotonergic antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), and does not resolve in most patients. Vortioxetine, an antidepressant with a multimodal mechanism of action, has shown low rates of sexual dysfunction in previous major depressive disorder (MDD) trials.

Aim. This study compared the effects of vortioxetine and escitalopram on sexual functioning in adults with well-treated MDD experiencing treatment-emergent sexual dysfunction (TESD).

Methods. Participants treated with, and responding to, citalopram, paroxetine, or sertraline were randomized to switch to either vortioxetine (10/20 mg; n = 225) or escitalopram (10/20 mg; n = 222) for 8 weeks. Sexual function was assessed using the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14), and antidepressant efficacy was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impressions (CGI) scale, and Profile of Mood States brief form (POMS-brief). Safety and tolerability were also assessed.

Main Outcome Measures. The primary endpoint was change from baseline in the CSFQ-14 total score after 8 weeks of treatment. The MADRS, CGI, and POMS-brief were used to assess antidepressant efficacy. Safety was assessed via adverse events, vital signs, electrocardiograms, laboratory values, weight, and physical examination findings.

Results. Vortioxetine showed significantly greater improvements in CSFQ-14 total score (8.8 ± 0.64, mean ± standard error) vs. escitalopram (6.6 ± 0.64; $P = 0.013$). Benefits vs. escitalopram were significant on four of five dimensions and all three phases of sexual functioning assessed by the CSFQ-14 ($P < 0.05$). Antidepressant efficacy continued in both groups, with similar, but slight, improvements in MADRS and CGI scores. Vortioxetine and escitalopram had similar clinical efficacy profiles in this study, with safety profiles similar to previous trials. Nausea (n = 9, 4.0%) was the most common treatment-emergent adverse event leading to discontinuation of vortioxetine.

Conclusion. Switching antidepressant therapy to vortioxetine may be beneficial for patients experiencing sexual dysfunction during antidepressant therapy with SSRIs. **Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, and Clayton AH. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. J Sex Med 2015;12:2036–2048.**

Key Words. Vortioxetine; Escitalopram; Major Depressive Disorder; Treatment-Emergent Sexual Dysfunction

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Trial dates: June 2011–December 2013

Introduction

Major depressive disorder (MDD) is estimated to affect about 16.6% of people in the United States at some time during their lives, and to affect 8.6% of people during a typical year [1]. Antidepressant drug therapy is the preferred treatment for moderate to severe depression [2]. Sexual dysfunction is a common symptom of depression [3], but it is also a common adverse effect of many antidepressant drugs, especially serotonin–norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) [4,5]. Sexual dysfunction associated with depression and SSRIs affects all phases of sexual activity, including desire, arousal, and orgasm [5–10]. Estimates of the percentage of patients on SSRIs who experience treatment-related sexual dysfunction have varied widely, but range from 25% to 80% depending on the method of assessment and number of sexual phases assessed [9,11,12]. Although successful treatment of depression may alleviate sexual dysfunction in some patients, the available evidence suggests that most patients treated with serotonergic antidepressants develop treatment-emergent sexual dysfunction (TESD) during treatment and continue to experience sexual dysfunction for prolonged periods [4,9–15]. Sexual dysfunction is also frequently cited as a cause for treatment discontinuation, leading to relapse of depression, although there is limited evidence supporting this claim.

Strategies for alleviating SSRI/SNRI-associated sexual dysfunction in patients being treated for MDD include reduction in medication dose, add-on therapy with agents that enhance dopamine levels (such as bupropion) or that affect specific serotonin receptors, switch to an antidepressant associated with less sexual dysfunction, or use of nonpharmacological approaches (such as exercise or yoga) [16–20]. Switching antidepressants because of sexual side effects is common and appears to be supported by indirect comparisons of clinical trial data, which have concluded that different antidepressants are associated with different rates of sexual dysfunction [11,21,22]. Furthermore, few randomized trials have explored the effectiveness of switching antidepressants for alleviating treatment-associated sexual dysfunction while maintaining effective treatment of depression.

Vortioxetine is an antidepressant agent approved in 2013 in the United States and Europe for treatment of MDD. It differs from preexisting antidepressants in that it combines two pharmacologic modes of action: direct modulation of receptor activity and inhibition of the serotonin transporter (SERT). Vortioxetine is an antagonist at 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors, an agonist at 5-HT_{1A} receptors, a partial agonist at 5-HT_{1B} receptors, and an inhibitor of the 5-HT transporter [23]. Several randomized, placebo-controlled trials in adults with MDD have found vortioxetine to be similar to placebo in rates of sexual dysfunction [24–29], making it a promising candidate for replacement therapy in patients experiencing TESD during SSRI treatment.

This paper reports on a randomized, double-blind clinical trial that enrolled adults with MDD who were who were effectively treated for depression with an SSRI (citalopram, paroxetine, or sertraline), but were reporting symptoms of TESD. These commonly prescribed SSRIs have been associated with higher rates of sexual dysfunction compared with other antidepressants, as reported in recent meta-analyses of clinical trials and observational studies of MDD patients [11,21,22]. During the double-blind treatment period of the current trial, patients were randomized to switch to either vortioxetine or escitalopram. Escitalopram is a widely used SSRI generally associated with moderate rates of sexual dysfunction according to recent meta-analyses [11,21], although one analysis found it to be associated with significantly higher rates than some other second-generation antidepressants [22]. In the current trial, both vortioxetine and escitalopram were initiated at a dose of 10 mg/day for 1 week, which was increased to 20 mg/day for the second week. For the remainder of the 8-week treatment period, the investigator could adjust the dose between 10 and 20 mg based on efficacy and tolerability. After 8 weeks of treatment, patients treated with escitalopram (10/20 mg) received 10 mg escitalopram for 1 additional week, in accordance with the package insert [30], whereas patients treated with vortioxetine (10/20 mg) received placebo.

Methods

Participants

Trial procedures were conducted at 66 sites in the United States and Canada. Eligible participants were men or women aged 18–55 years, with this age range chosen as rates of primary sexual dysfunction—and comorbid conditions or treatments associated with TESD—are known to increase with age. All patients were required to be

on a stable SSRI treatment regimen for a major depressive episode (MDE) diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) as assessed by the Mini International Neuropsychiatric Interview (MINI), Version 6.0.0 [31]. Allowed treatment regimens were monotherapy with citalopram, paroxetine, or sertraline. The treatment and dosage had to have been stable for at least 8 weeks prior to randomization, and eligible participants had to have depression symptoms that were stable as judged by the investigator and as indicated by Clinical Global Impressions–Severity of Illness (CGI-S) [32] scores of 3 or less at screening and baseline visits. In addition, all eligible participants had to have been sexually active at least every 2 weeks before onset of the current MDE and/or SSRI use and had to be experiencing symptoms of sexual dysfunction attributed to their current SSRI treatment. To confirm the diagnosis of TESD and evaluate the severity of baseline sexual dysfunction, patients enrolled in the study were required to have a total score of 41 or less for women and 47 or less for men on the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14 [33]; available at http://www.proqolid.org/instruments/changes_in_sexual_functioning_questionnaire_csfq). The CSFQ-14 is a 14-item version of the original CSFQ, which was developed with specific versions for women and men to assess sexual functioning in all the domains of the sexual response cycle. It was developed to be used in both clinical and research settings [34]. The CSFQ-14 yields scores for three scales corresponding to the phases of the sexual response cycle (i.e., desire, arousal, and orgasm) as well as the five scales of the original CSFQ (sexual desire, sexual frequency, sexual satisfaction, sexual arousal, and sexual completion).

Participants had to be suitable candidates for switching antidepressant therapy according to the investigator's judgment. Female participants of childbearing potential had to agree to use adequate contraception throughout the trial. During screening, individuals were ruled ineligible for participation if they had sexual dysfunction—including men with a history of premature ejaculation in the preceding year—associated with an etiology other than SSRI use or MDE; had a major relationship change preceding SSRI treatment or were planning such a change; were planning (or their partner was planning) to initiate treatment for sexual dysfunction during the study; or had any concurrent psychiatric or neurologic disorder other than MDD, had a recent diagnosis of alcohol or substance abuse, or were receiving excluded medications or treatments.

The trial was conducted according to the World Medical Association Declaration of Helsinki, the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, and all applicable federal, local, or regional regulatory requirements. An ethics committee for each site approved the protocol, and written consent was obtained from each participant before any study procedures were performed. The trial was conducted from June 2011 to December 2013 and is registered with ClinicalTrials.gov (NCT01364649).

Study Procedures and Outcome Measures

A diagram of the study timeline is shown in Figure 1. Screening procedures were conducted from 2 weeks prior to 1 week prior to baseline, including screening in accordance with predefined inclusion/exclusion criteria, physical examination, and complete medical history. At the baseline visit (day 0), enrolled participants discontinued their

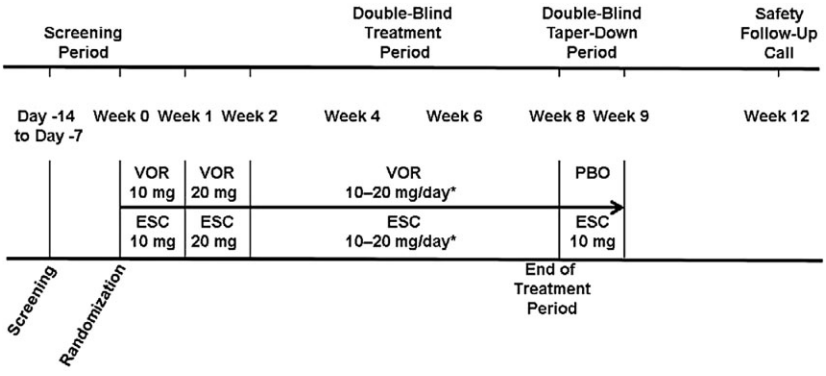

Figure 1 Schematic of study design. *Both arms allowed dose reduction to 10 mg/day and adjusted back up to 20 mg/day as tolerated for weeks 2, 4, and 6, based on investigator judgment. ESC = escitalopram; PBO = placebo; VOR = vortioxetine.

current antidepressant medication and were randomly assigned to switch antidepressant therapy to either vortioxetine or escitalopram (1:1 allocation), with no break in therapy. Participants in both arms received 10 mg/day of allocated study drug for 1 week, then 20 mg/day for the second week. During the remainder of the 8-week double-blind treatment period, participants received study drug at doses of 10 or 20 mg with doses adjusted at the end of weeks 2, 4, and 6 at the investigator's discretion. After completion of the double-blind treatment period (or at the time of study discontinuation), participants in the vortioxetine group received placebo daily and participants in the escitalopram group received 10 mg/day escitalopram for 1 week in a double-blind manner to allow for taper down as per the current package insert for escitalopram [30]. Escitalopram oxalate tablets (Lexapro; Forest Laboratories, Inc., St. Louis, MO, USA) were purchased and were over-encapsulated to be indistinguishable from vortioxetine capsules.

Assessments were performed during clinic visits at baseline, at the end of weeks 1, 2, 4, 6, and 8, and at the end of the taper-down period (end of week 9). A follow-up phone call for safety monitoring was performed at week 12. Sexual functioning was assessed at each clinic visit using the CSFQ-14—a 14-item self-reported patient outcome measure with the total score ranging from 14 to 70 and with higher scores indicating higher functioning [35]. Antidepressant efficacy was assessed at each clinic visit using the Montgomery-Åsberg Depression Rating Scale (MADRS) [36] and the Clinical Global Impressions (CGI) scale, including the severity of illness (CGI-S) and improvement (CGI-I) subscales [32]. Participants also completed the Profile of Mood States brief form (POMS-brief) [37] and were assessed for suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS) [38] at each clinic visit. Participants were assessed for adverse events by clinical laboratory tests, 12-lead electrocardiograms, physical examination, and vital signs.

The primary endpoint was change from baseline in CSFQ-14 total score at the end of the 8-week, double-blind treatment period. Secondary endpoints included change from baseline in CSFQ-14 total scores at individual clinic visits; the number of participants whose CSFQ-14 total scores shifted from abnormal (41 or less for women and 47 or less for men) to normal at each visit; and CSFQ-14 responder rates (response defined as an increase from baseline in CSFQ-14 total score of at least 3 points). Changes in the CSFQ-14 total score of 2–3 points are considered clinically meaningful based on differences in total score seen between SSRIs and placebo groups [6], SSRIs and drugs not likely to cause sexual dysfunction (such as bupropion) in spontaneous patient reporting of sexual functioning [39], as well as the clinical experience of the scale developer. Because a change in total score of 2–3 points is considered clinically meaningful, a CSFQ-14 response was defined as a change in the total score that was greater than or equal to 3 points. Other endpoints included change from baseline in CSFQ-14 subscales, change from baseline in MADRS total score, CGI-I score, change from baseline in CGI-S score, and change from baseline in POMS-brief total score. Predefined secondary analyses included assessment of efficacy by age, gender, and disease severity. Suicidality assessment was conducted in a prespecified manner by summary statistics for the C-SSRS.

Randomization, Sample Size, and Statistical Procedures

The randomization schedule was generated and maintained securely by Takeda Global Research and Development. At the time of randomization, investigators obtained a participant's study medication assignment through an interactive voice-response system that maintained blinding. The sample size was calculated assuming a standard deviation of 8.5 for change from baseline in CSFQ-14 total score and a 15% dropout rate. A sample size of 220 participants per group was estimated to achieve 80% power to detect a difference of 2.5 points between the two treatment groups in the primary endpoint of change from baseline in CSFQ-14 total score at week 8. No statistical corrections were made to control for multiple comparisons.

Primary and secondary endpoints were analyzed using data from the full analysis set (FAS), which included all participants who were randomized, received at least one dose of study drug, and had at least one valid post-baseline value for assessment of the primary endpoint. Safety was assessed among all participants who were randomized and received at least one dose of study medication.

The primary endpoint, change from baseline to week 8 in CSFQ-14 total score, was analyzed using observed cases (OC) and a mixed model for repeated measures (MMRM) analysis of covariance with treatment, week, and treatment-by-week interaction as fixed effects, baseline CSFQ-14 total

Table 1 Disposition of enrolled participants, reasons for withdrawal, and study populations used in data analyses

	Number of patients, N (%)	
	Vortioxetine	Escitalopram
Number of patients randomized	225	222
Completed study	169 (75.1%)	179 (80.6%)
Prematurely discontinued	56 (24.9%)	43 (19.4%)
Reason for withdrawal		
Adverse events	20 (8.9%)	14 (6.3%)
Lack of efficacy†	6 (2.7%)	0
Lost to follow-up	12 (5.3%)	13 (5.9%)
Non-compliance	1 (0.4%)	0
Protocol deviation	4 (1.8%)	8 (3.6%)
Withdrawal of consent	9 (4.0%)	7 (3.2%)
Other	4 (1.8%)	1 (0.5%)
Safety population	224	221
Full analysis population‡	217	207
Per-protocol population‡	192	195

†Lack of efficacy possibly as a result of the change in treatment from a selective serotonin reuptake inhibitor (SSRI) to vortioxetine. ‡10 patients (6 escitalopram and 4 vortioxetine) were administered the incorrect version of the Changes in Sexual Functioning Questionnaire at baseline and/or during study. Specifically, either an outdated version of the scale was used, or the wrong gender form was administered. These patients were excluded from the efficacy analysis.

score-by-week as covariate, and a completely unstructured covariance matrix. Responder rates—a response was defined as an increase from baseline in CSFQ-14 total score of at least 3 points—and shifts to normal sexual function were analyzed using logistic regression adjusted for baseline CSFQ-14 score and treatment, using both the method of last-observation carried forward (LOCF) and OC. C-SSRS data were analyzed using descriptive statistics and a shift-table. Other secondary endpoints were also analyzed by MMRM similar to the primary endpoint. All statistic tests were two-sided with a 0.05 significance threshold. Statistic analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA).

Results

In total, 711 individuals were screened, 447 met criteria for inclusion and were randomized, and 348 completed the study. Disposition of randomized participants and data sets used for analyses are shown in Table 1. The majority of patients received the highest approved doses of study drug from weeks 2 to 8 (vortioxetine 20 mg, 75.9%; escitalopram 20 mg, 81.4%). Twenty participants (8.9%) in the vortioxetine group and 14 (6.3%) in the escitalopram group withdrew because of an adverse event. Two participants, one in each arm, were randomized but did not receive study drug and are not included in any analysis sets. Ten participants (four vortioxetine, six escitalopram) were administered the incorrect version of the CSFQ-14 assessment during the study and are not included in efficacy analyses (Figure 2). Demographic and baseline characteristics of randomized participants are shown in Table 2. Both groups were comparable and exhibited evidence of remission from depression as indicated by mean baseline CGI-S

Table 2 Demographic and baseline characteristics of enrolled participants

	Vortioxetine N = 225	Escitalopram N = 222
Age (years)		
Mean ± SD	39.3 ± 9.96	40.2 ± 10.01
Range	19–55	19–55
Gender, N (%)		
Male	97 (43.1)	87 (39.2)
Female	128 (56.9)	135 (60.8)
Race, N (%)		
Caucasian	178 (79.1)	181 (81.5)
Black	41 (18.2)	35 (15.8)
Asian	4 (1.8)	3 (1.4)
Other	2 (0.9)	3 (1.4)
Weight (kg)		
Mean ± SD	79.6 ± 16.20	81.2 ± 16.01
BMI (kg/m^2)		
Mean ± SD	27.5 ± 4.35	27.9 ± 4.44
Smoking history, N (%)		
Never smoked	112 (49.8)	126 (56.8)
Current smoker	69 (30.7)	55 (24.8)
Previous smoker	44 (19.6)	41 (18.5)
Number of previous MDEs, N (%)		
1–3	144 (64.0)	149 (67.1)
4–6	33 (14.7)	29 (13.1)
>6	5 (2.2)	1 (0.5)
Duration of current MDE (weeks)		
Mean ± SD	102.8 ± 153.10	109.3 ± 150.11
Current pharmacotherapy, N (%)		
Citalopram	120 (53.3)	115 (51.8)
Paroxetine	36 (16.0)	30 (13.5)
Sertraline	69 (30.7)	77 (34.7)
CSFQ-14 total score		
Mean ± SD	36.5 ± 5.81	36.3 ± 5.62
Range	21–47	21–47
CSFQ-14 total score, males		
Mean ± SD	39.8 ± 5.38	40.5 ± 4.03
CSFQ-14 total score, females		
Mean ± SD	33.9 ± 4.73	33.6 ± 4.94
CSFQ-14 total score, aged ≤41		
Mean ± SD	36.3 ± 5.67	35.6 ± 5.90
CSFQ-14 total score, aged >41		
Mean ± SD	36.4 ± 5.95	36.9 ± 5.37
MADRS total score		
Mean ± SD	7.9 ± 6.28	8.3 ± 6.53
Range	0–34	0–34
CGI-S score		
Mean ± SD	2.0 ± 0.81	2.0 ± 0.84
Range	1–3	1–3
POMS-brief total score		
Mean ± SD	18.8 ± 19.36	19.7 ± 19.45
Range	−12–80	−13–76

BMI = body mass index; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short Form; MADRS = Montgomery-Åsberg Depression Rating Scale; MDE = major depressive episode; POMS-brief = Profile of Mood States brief form; SD = standard deviation.

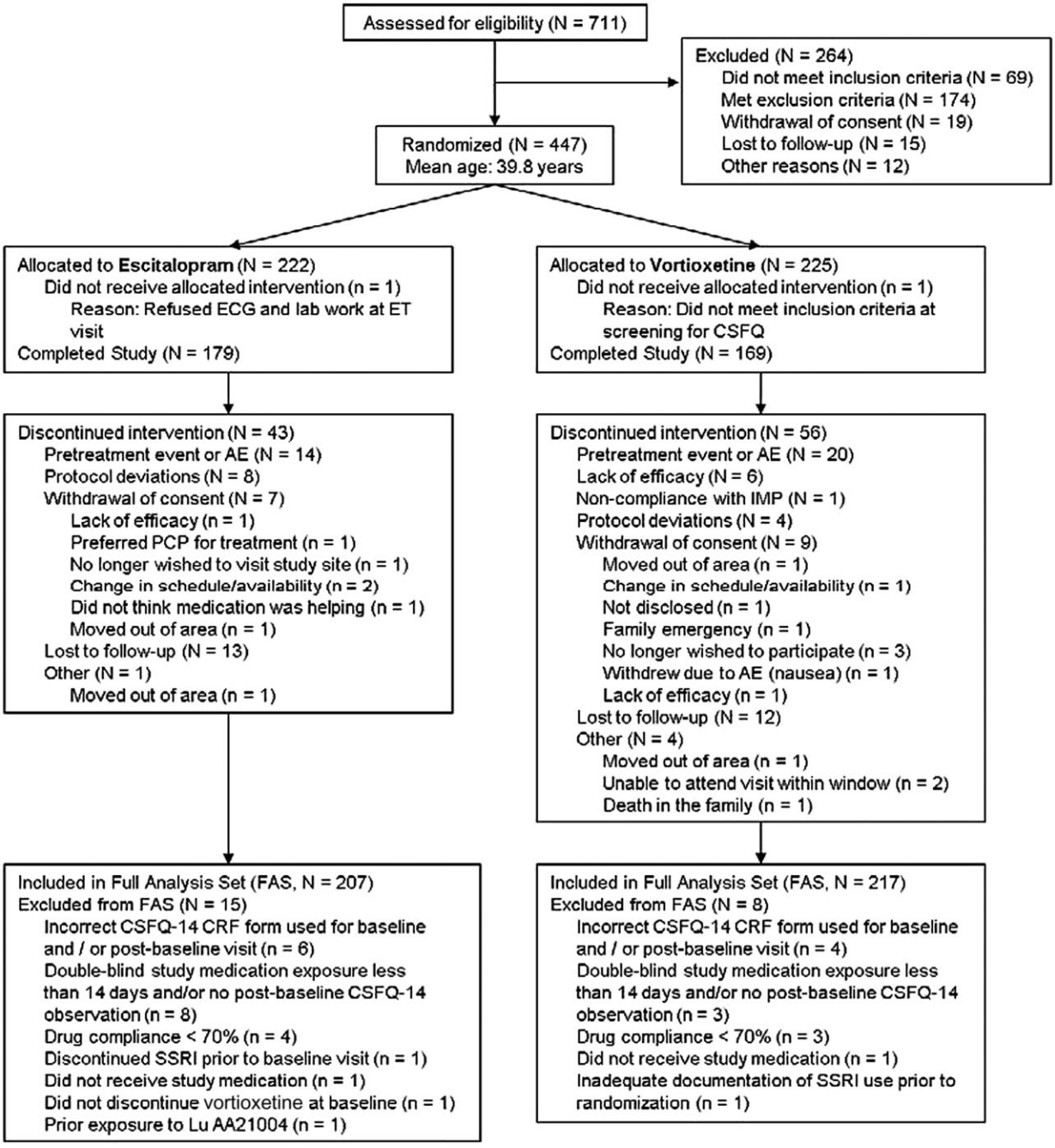

Figure 2 Study Flow and CONSORT diagram. AE = adverse event; CRF = case report form; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short Form; ECG = electrocardiogram; ET = early termination; FAS = full analysis set; PCP = primary care physician; SSRI = selective serotonin reuptake inhibitor.

scores of 3 or less, and evidence of sexual dysfunction as indicated by mean baseline CSFQ-14 scores.

Sexual Functioning

Changes from baseline in CSFQ-14 total score during the 8-week double-blind treatment period are shown in Figure 3. Mean increases in CSFQ-14 total score were significantly greater in the vortioxetine group (8.8 ± 0.64; least squares [LS] mean ± standard error) than in the escitalopram group (6.6 ± 0.64; $P = 0.013$). The vortioxetine group also had significantly greater mean increases in CSFQ-14 total score than did the escitalopram

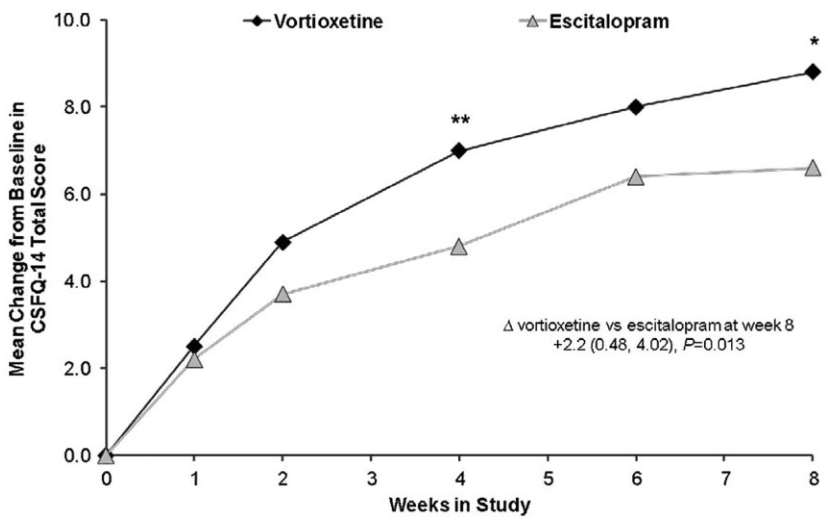

Figure 3 Mean changes from baseline in Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14) total scores during the double-blind treatment period. MMRM, FAS, LS means. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. escitalopram.

group at week 4 (7.0 ± 0.55 vs. 4.8 ± 0.55; $P = 0.004$) and numerically greater increases at week 6, but the difference at week 6 was not statistically significant (8.0 ± 0.59 vs. 6.4 ± 0.60; $P = 0.057$). Normal sexual functioning at the end of the treatment period (defined as CSFQ-14 score greater than 41 for women and greater than 47 for men) was achieved by 52.1% of patients treated with vortioxetine and 44.2% of patients treated with escitalopram (odds ratio [OR] = 1.37; $P = 0.112$). Similarly, a clinically relevant response on the CSFQ-14 (predefined as an increase from baseline in CSFQ-14 total score of at least 3 points at the end of week 8) was achieved by 74.7% of those patients receiving vortioxetine and 66.2% of those receiving escitalopram (OR = 1.50; $P = 0.057$).

Although the trial was not powered to detect treatment differences in subgroups of participants, greater improvements in CSFQ-14 total scores were observed in subgroups defined by gender, age, and CGI-S score at baseline when these patient subgroups were treated with vortioxetine vs. escitalopram. However, the difference between vortioxetine and escitalopram was statistically significant only in men (the improvement for vortioxetine over escitalopram in women did not reach statistical significance; $P = 0.062$), in participants aged 41 years or younger (as compared with those older), and in participants with baseline CGI-S scores of 2 or less (as compared with those having scores greater than 2) (Figure 4). Analysis of CSFQ-14 subscores (Figure 5) revealed that participants in the vortioxetine group exhibited signifi-

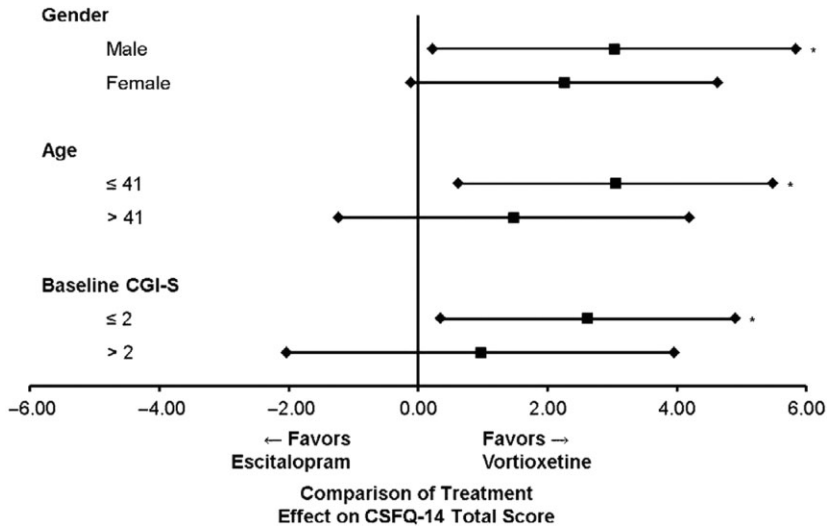

Figure 4 Mean (95% confidence interval) differences between vortioxetine and escitalopram groups in change from baseline in Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14) total score at week 8 in subgroups defined by gender, age, and baseline Clinical Global Impressions-Severity (CGI-S) score. MMRM, FAS, LS means. $^{*}P < 0.05$ vs. escitalopram.

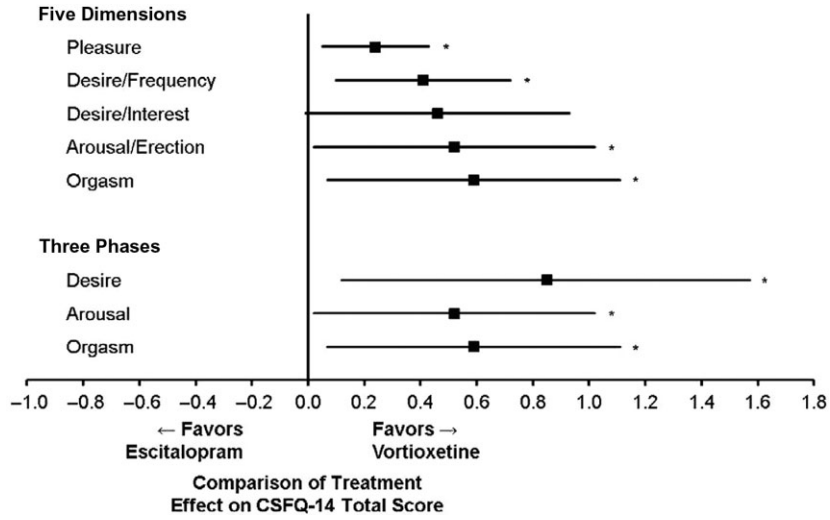

Figure 5 Mean (95% confidence interval) differences between vortioxetine and escitalopram groups in the five dimensions and three phases of sexual function included in the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14) assessment. MMRM, FAS, LS means. *$P < 0.05$ vs. escitalopram.

cantly greater improvements during the treatment period in four of five dimensions and in all three phases of sexual functioning ($P < 0.05$) as compared with the escitalopram group.

Maintenance of Antidepressant Efficacy

The effects of vortioxetine and escitalopram on measures of depression severity during the double-blind treatment period are shown in Figure 6. Both the vortioxetine and escitalopram groups exhibited small reductions in mean MADRS total score (Figure 6A) during the treatment period; there were no statistically significant differences or clinically relevant differences between the treatment arms. Mean CGI-I scores (Figure 6B) also showed slight reductions, suggesting a trend toward greater improvement of depressive symptoms during study treatment. CGI-S scores did not change substantially at week 8 (-0.1 ± 0.04; -0.1 ± 0.04, $P = 0.355$ [MMRM, FAS]), and on average, patients self-reported slight improvements in mood symptoms on the POMS-brief at week 8 (-5.6 ± 1.18; -6.9 ± 1.18, $P = 0.42$ [MMRM, FAS]). Differences in the percentage of patients in remission at week 8—as indicated by a MADRS score of 10 or less (78.7%; 77.3%, $P = 0.902$) and a CGI-S score of 2 or less (76.0%; 71.5%, $P = 0.316$)—were not significant.

Safety

A summary of adverse events occurring after initiation of study treatment is shown in Table 3. Most adverse events were mild or moderate in severity. There were six serious adverse events: three patients experienced a total of five serious adverse events in the vortioxetine group (angina pectoris, depression [in two patients], anxiety, and nephrolithiasis) and one patient in the escitalopram group reported one serious adverse event (mesenteric vein thrombosis). Only nephrolithiasis and mesenteric artery thrombosis were considered by investigators to be possibly related to study drug. During the treatment period, there was one case of "interrupted, aborted, or preparatory acts or behavior" related to suicide in the

Table 3 Summary of adverse events during the double-blind treatment period

	Number of patients	
	Vortioxetine N = 224	Escitalopram N = 221
Adverse event overview		
Any adverse event	146 (65.2%)	137 (62.0%)
Related adverse events	120 (53.6%)	104 (47.1%)
Adverse events leading to withdrawal	21 (9.4%)	14 (6.3%)
Serious adverse events[†]	3 (1.3%)	1 (0.5%)
Adverse events leading to withdrawal in ≥2 patients		
Nausea	9 (4.0%)	0
Depression	1 (0.4%)	3 (1.4%)
Anxiety	1 (0.4%)	1 (0.5%)
Insomnia	1 (0.4%)	1 (0.5%)
Vomiting	2 (0.9%)	0
Most frequent adverse events (incidence ≥5.0%)		
Nausea	56 (25.0%)	12 (5.4%)
Headache	21 (9.4%)	17 (7.7%)
Dizziness	18 (8.0%)	11 (5.0%)
Pruritus, generalized	13 (5.8%)	0
Irritability	11 (4.9%)	16 (7.2%)
Fatigue	10 (4.5%)	12 (5.4%)
Anxiety	5 (2.2%)	12 (5.4%)

[†]Investigator judgment.

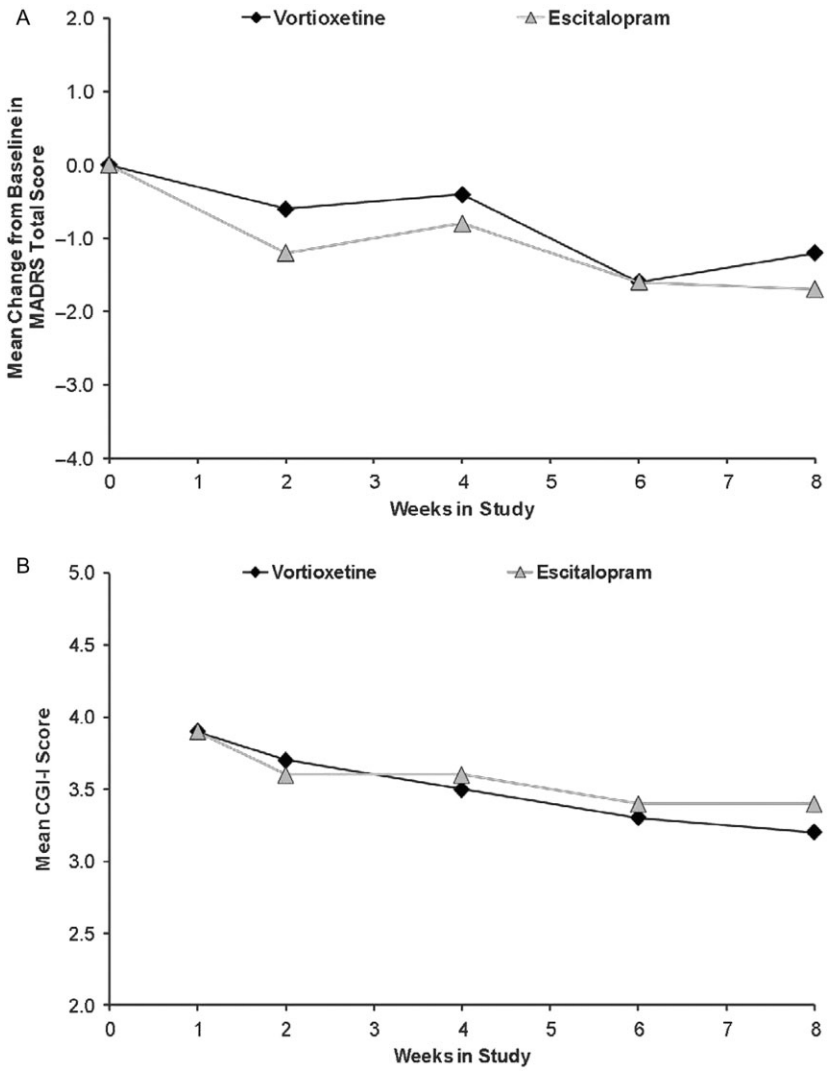

Figure 6 Mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score (A) and mean Clinical Global Impressions-Improvement (CGI-I) score (B) for vortioxetine and escitalopram groups during the double-blind treatment period.

vortioxetine group as assessed by the C-SSRS, but no attempted or completed suicides. There were no deaths reported for any reason during the study.

Vortioxetine was associated with a substantially higher number of participants experiencing nausea (25.0% vs. 5.4%), with the incidence of nausea for vortioxetine consistent with data from previous trials and the rate for escitalopram notably lower than reported in the package insert (15.0%) [30]. In addition, nine patients withdrew because of nausea in the vortioxetine group vs. none in the escitalopram group. As seen in previous trials with vortioxetine, most cases of nausea in this trial were transient, lasting a median of 7.0–7.5 days. Vortioxetine was also associated with substantially more cases of generalized pruritus (n = 13, 5.8%), although only one case was severe in intensity and none resulted in withdrawal. Escitalopram was associated with nine patients spontaneously reporting specific adverse events associated with sexual dysfunction, including decreased libido (n = 5), anorgasmia, delayed ejaculation, failed ejaculation, abnormal orgasm, disturbance in sexual arousal, and erectile dysfunction (all n = 1). No patients treated with vortioxetine spontaneously reported any adverse events associated with sexual dysfunction.

Discussion

Sexual dysfunction is a common side effect of SSRI and SNRI therapies for MDD and only occasionally resolves during continued use of these agents. The current randomized, double-blind trial demonstrated that switching from an SSRI (citalopram, paroxetine, or sertraline) to the

antidepressant vortioxetine was associated with significant clinical improvements in sexual functioning in well-treated MDD patients who were experiencing SSRI-related sexual dysfunction—as evidenced by baseline CSFQ-14 scores of 41 or less for women and 47 or less for men—with no loss of clinical efficacy. The improvements in sexual functioning observed in vortioxetine-treated patients were significantly greater than those observed in the escitalopram-treated group. Although escitalopram is an SSRI, it has been associated with less sexual dysfunction than citalopram, paroxetine, or sertraline [11,21]; this observation was also supported by the results of this study as those patients in the escitalopram group demonstrated some improvement in sexual functioning. Overall, almost 75% of participants in the vortioxetine group showed an improvement of 3 or more points in the CSFQ-14 total score compared with 66.2% of escitalopram-treatment patients, above the threshold for clinical improvement [35]. Furthermore, 52.1% of patients switched to vortioxetine met the criteria for normal sexual function at the end of the treatment period, compared with 44.2%of escitalopram-treated patients. Clinically relevant improvements in sexual functioning for vortioxetine-treated patients were seen as early as week 2 compared with escitalopram, with continued improvement over the course of the 8-week study. The benefits of vortioxetine over escitalopram on sexual function were observed on four of five dimensions and three phases of sexual functioning, demonstrating statistically significant improvements for the vortioxetine vs. escitalopram groups. The dimension of desire/interest showed meaningful improvement over escitalopram, but did not reach statistical significance ($P = 0.106$). The results from this clinical study support the results from a recent pooled analysis of more than 1,100 patients in the vortioxetine clinical development program, where the risk of developing TESD as assessed by the Arizona Sexual Experiences Scale in patients without sexual dysfunction at baseline was not statistically significantly different between vortioxetine (5–20 mg/day) and placebo, with noninferiority demonstrated for 5 mg [40].

Antidepressant efficacy must be maintained if antidepressant medication is to be successfully switched to alleviate sexual dysfunction. In the current trial, depressive symptoms were required to be well treated (according to the investigator's judgment and a CGI-S score of 3 or less) at baseline. The severity of depressive symptoms for both vortioxetine-treated and escitalopram-treated participants, as measured by MADRS and CGI scores, remained low and even improved slightly during the double-blind treatment period. Similar improvements in mood symptoms were also noted on the POMS-brief at week 8 for both compounds. The results of the current study support the findings of the recently published study by Montgomery et al. where MDD patients with an inadequate response to previous SSRI/SNRI treatment were safely and effectively switched to vortioxetine [41].

The dose range of escitalopram chosen as comparator (10/20 mg/day) represents approved doses that have demonstrated efficacy in the acute and maintenance treatment of MDD [42–45]. The current trial confirms the efficacy of vortioxetine and escitalopram where patients were switched to either drug while being well treated with an SSRI, with the majority of patients receiving the highest approved doses of vortioxetine or escitalopram. Furthermore, the trial demonstrated comparable efficacy of the two drugs for maintenance of efficacy after a switch. The superior improvements in sexual functioning among patients switched to vortioxetine vs. escitalopram may improve compliance with therapy, although this was not tested in the current study.

Patients in the vortioxetine group experienced more nausea vs. escitalopram during the initial 2 weeks of treatment. Although the rate of nausea in the vortioxetine group was consistent with prior trials, the rate in the escitalopram group was lower than seen in recent clinical trials. Consistent with prior trials, most cases of nausea associated with vortioxetine were transient, with a median duration of 7 to 7.5 days. One factor that may contribute to nausea in the vortioxetine group is the potential incidence of SSRI discontinuation syndrome because of switching from previous SSRI therapies, given that less than 50% of vortioxetine's clinical effect is due to SERT inhibition [46]. SSRI discontinuation syndrome was not expected in patients who switched to escitalopram from previous SSRIs, as the level of SERT inhibition with escitalopram is greater than 80% [47–49]. Further studies are required to understand this issue. Comparatively lower rates of nausea in patients receiving escitalopram may be due to the majority of patients being previously stabilized on citalopram therapy (vortioxetine, 51.8%; escitalopram, 53.3%), with low rates of nausea expected in patients who switched from citalopram to escitalopram.

Although SSRI treatment of depression can bring improvements in sexual desire and satisfaction [6,50], most cases of sexual dysfunction in patients with MDD continue unresolved, even during antidepressant treatment [9,13]. Treatment-associated sexual dysfunction may adversely affect self-esteem, interpersonal relationships, and quality of life [51]. Furthermore, it is often cited as a cause of noncompliance and as a major factor in the failure of antidepressant therapy [20], although controlled studies are lacking. Effective antidepressant therapies that do not adversely impact sexual functioning remain an important unmet need.

The current trial evaluated only 8 weeks of therapy with vortioxetine or escitalopram, so it does not establish that improvements in sexual functioning will continue during long-term treatment—a similarly designed long-term trial would be required to evaluate long-term clinical benefits. However, vortioxetine has been effective in preventing relapse of MDD during long-term therapy (up to 76 weeks) in patients who responded to initial therapy, with a very low incidence of sexual side effects [52]. In studies of other antidepressants (including escitalopram), although remission is often achieved, sexual dysfunction generally appears within the first two weeks of therapy and resolves in only 5% to 10% of patients after 4 to 6 months of continued antidepressant use [9].

This study has certain limitations arising from the trial design, which may affect its generalizability. Limiting enrollment to patients aged 18 to 55 years and excluding patients with other comorbid conditions, concurrent psychiatric conditions, and alcohol/substance abuse limits application of its conclusions to these relevant patient populations. The study did not include other classes of antidepressants, so the comparative impact on TESD of vortioxetine vs. other antidepressants, including SNRIs (such as duloxetine or venlafaxine), tricyclic antidepressants, and monoamine oxidase inhibitors, cannot be determined.

For patients with MDD who are responding to SSRI therapy, but are experiencing TESD, switching antidepressant therapy to vortioxetine (10/20 mg/day) was associated with significant improvements in sexual functioning for both male and female patients (with significantly greater improvements observed in male patients) compared with those who were switched to escitalopram (10/20 mg/day). The benefits of vortioxetine were observed across a broad range of sexual dimensions and phases, including pleasure, desire, arousal, and orgasm. Both drugs maintained antidepressant efficacy and even showed evidence of further improvements in depression scale scores. Although vortioxetine was associated with higher rates of nausea than escitalopram that resulted in discontinuation in a small number of patients, this side effect was transient in most patients. Switching antidepressant therapy to vortioxetine may be an alternative for patients experiencing sexual dysfunction during antidepressant therapy with an SSRI.

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