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Sexual dysfunction during treatment of major depressive disorder with vilazodone, citalopram, or placebo: results from a phase IV clinical trial

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Sexual dysfunction commonly occurs with major depressive disorder (MDD). Vilazodone, a selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist antidepressant approved for the treatment of MDD in adults, was evaluated to determine its effects on sexual function. The primary study was a double-blind, randomized, controlled trial comparing vilazodone 20 and 40 mg/day with placebo; citalopram 40 mg/day was an active control (NCT01473381; *http://www.clinicaltrials.gov*). Post-hoc analyses evaluated change from baseline to week 10 on the Changes in Sexual Functioning Questionnaire (CSFQ); no inferential statistics were performed. CSFQ scores increased for women [1.2 (citalopram) to 3.0 (vilazodone 40 mg)] and men [1.2 (vilazodone 40 mg) to 3.5 (placebo)] in all treatment groups. Greater changes in CSFQ scores were seen in responders [women: 2.33 (citalopram) to 5.06 (vilazodone 40 mg); men: 2.26 (vilazodone 40 mg) to 4.35 (placebo)] versus nonresponders. CSFQ change from baseline was small for patients with normal baseline sexual function; in patients with baseline sexual dysfunction, CSFQ scores improved across groups [women: 2.35 (citalopram) to 4.52 (vilazodone 40 mg); men 2.83 (vilazodone 40 mg) to 6.43 (placebo)]. Across treatment groups, baseline sexual function improved in women and men, MDD responders, and patients with baseline sexual dysfunction. *Int Clin Psychopharmacol* 30:216–223

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Introduction

Sexual dysfunction and major depressive disorder (MDD) appear to have a bidirectional relationship, (Atlantis and Sullivan, 2012) with sexual dysfunction increasing the risk of depression, and depression and its treatment frequently being cited as causes of sexual dysfunction. Up to 60% of patients treated with selective serotonin reuptake inhibitors (SSRIs) report some sexual dysfunction (Kennedy and Rizvi, 2009). A leading cause of nonadherence to antidepressants, (Ashton *et al.*, 2005) sexual dysfunction is considered by patients to be one of the most unacceptable side effects of SSRI treatment (Hu *et al.*, 2004). Strategies to improve sexual function during antidepressant treatment include lowering drug dosage, switching to a new antidepressant from the same or a different class, or adding a new agent such as buspirone (a 5-HT_{1A} partial agonist), bupropion (a norepinephrine-dopamine reuptake inhibitor), or a cGMP-specific phosphodiesterase type 5 inhibitor (e.g. sildenafil, tadalafil). Successful management of the complex interrelationship between sexual dysfunction, depression, and antidepressant therapy is needed to improve clinical outcomes.

Vilazodone is an SSRI and 5-HT_{1A} receptor partial agonist approved by the US Food and Drug Administration for the treatment of MDD in adults. The efficacy of vilazodone 40 mg/day was established in two short-term, double-blind, placebo-controlled phase III trials (NCT00285376 and NCT00683592) (Rickels *et al.*, 2009; Khan *et al.*, 2011). In both studies, significantly greater improvement was seen for vilazodone 40 mg/day versus placebo on the primary efficacy parameter, mean change from baseline to week 8 in Montgomery–Åsberg Depression Rating Scale (MADRS) total score (Montgomery and Asberg, 1979). Safety and tolerability findings were supported in a 1-year, open-label trial of vilazodone 40 mg/day (NCT00644358) (Robinson *et al.*, 2011). In these three studies, sexual functioning was assessed by the Changes in Sexual Functioning Questionnaire (CSFQ) (Clayton *et al.*, 1997) or the Arizona Sexual Experience Scale (Mcgahuey *et al.*, 2000). Prospectively defined outcomes in these studies showed

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that treatment with vilazodone 40 mg/day was associated with improvement from baseline in sexual function and limited adverse impact on sexual function relative to placebo (Clayton *et al.*, 2013). In addition, in preclinical studies in rodent models, vilazodone, unlike the SSRIs citalopram and paroxetine, was not associated with sexual dysfunction in male rats (i.e. ejaculation frequency and/or copulatory efficiency) (Oosting *et al.*, 2013).

In a recent phase IV study (NCT01473381; *http://www.clinicaltrials.gov*) (Mathews *et al.*, 2015), the efficacy, safety, and tolerability of vilazodone 20 and 40 mg/day versus placebo were evaluated in patients with MDD; the SSRI citalopram was included as an active control for assay sensitivity. Mean change in MADRS total score from baseline at week 10, the primary efficacy parameter, was significantly greater in vilazodone 20 mg/day ($P=0.0073$) and 40 mg/day ($P=0.0034$) patients versus placebo patients; citalopram patients also had a significantly ($P=0.0020$) greater decrease in MADRS total score compared with placebo. Both vilazodone doses and citalopram were generally well tolerated. The effect of vilazodone on sexual functioning was prospectively measured by CSFQ mean score change from baseline to week 10. The CSFQ is a 14-item self-report scale comprising different domains that evaluate various phases of the sexual cycle; the CSFQ is frequently used to measure changes in sexual function related to the effects of antidepressant treatment, with lower scores indicating worse sexual functioning (Clayton *et al.*, 2014). Results from the prospective analyses indicated improved sexual functioning in each treatment group, with no statistically significant between-group differences.

Post-hoc analyses of CSFQ data from the phase IV study conducted from December 2011 through March 2013 were used to further characterize the effects of vilazodone on sexual function in adult patients with MDD. Analyses were conducted on patient subgroups to evaluate men and women, patients with normal sexual function and baseline sexual dysfunction, and MADRS responders versus nonresponders. Analysis of CFSQ domains allowed for sex-specific evaluation of the different phases of the sexual cycle. Because citalopram was included as an active control, the effects of this SSRI on sexual function were noted; however, the study was not powered to make direct comparisons between treatment groups.

Methods

Primary study design

The primary study (NCT01473381) (Mathews *et al.*, 2015) was a multicenter, randomized, double-blind, placebo-controlled and active-controlled, parallel-group, fixed-dose study comparing vilazodone 20 and 40 mg/day with placebo; citalopram 40 mg/day was included as an active control. The study comprised a 1- to 4-week no-drug screening period, 10-week double-blind treatment, and 1-week double-blind down-taper. Eligible patients were randomized by computer-generated numbers (1 : 1:1 : 1) to placebo, vilazodone 20 mg/day, vilazodone 40 mg/day, or citalopram 40 mg/day. The MADRS was administered at screening and weeks 0 (baseline), 1, 2, 4, 6, 8, and 10. The CSFQ was a protocol-specified outcome measure that was administered at weeks 0, 4, 8, and 10; CSFQ total score mean change from baseline to week 10 was analyzed using a mixed-effects model for repeated measures. CSFQ analyses were based on the CSFQ analysis population (patients with baseline and ≥ 1 postbaseline CSFQ assessment); safety analyses were based on the safety population (all randomized patients who received ≥ 1 dose of double-blind study drug).

Patient selection

Adult male and female outpatients (18–70 years of age, inclusive) who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) (American Psychiatric Association, 2000) criteria for MDD, with an ongoing major depressive episode of at least 8 weeks and up to 12 months and a MADRS total score at least 26 were included. Key exclusion criteria included DSM-IV-TR-defined axis I disorder other than MDD, suicide risk, and nonresponse to at least two antidepressants after adequate treatment trials. Use of psychoactive drugs or required concomitant treatment with certain medications was prohibited; eszopiclone, zopiclone, zaleplon, zolpidem, or zolpidem extended release were allowed for insomnia.

Post-hoc analyses of sexual function and depression

Post-hoc analyses evaluated CSFQ mean score change from baseline to week 10 in male and female patient subgroups; relative to MADRS response status (MADRS response was defined as $\geq 50\%$ improvement from baseline to end of treatment using the last observation carried forward approach); and in patients with and without baseline sexual dysfunction. CSFQ subscales evaluated five domains and three phases of sexual function plus satisfaction: pleasure, desire/frequency, desire/interest, arousal, and orgasm. CSFQ total scores range from 14 to 70, with baseline sexual dysfunction defined as CSFQ total score up to 47 for male patients and up to 41 for female patients (Clayton *et al.*, 1997). Sexual dysfunction during double-blind treatment was defined as CSFQ scores up to 47 (men) or up to 41 (women) for at least two consecutive visits during double-blind treatment. Post-hoc results were reported using descriptive statistics; no inferential statistical analyses were performed.

Adverse events related to sexual function

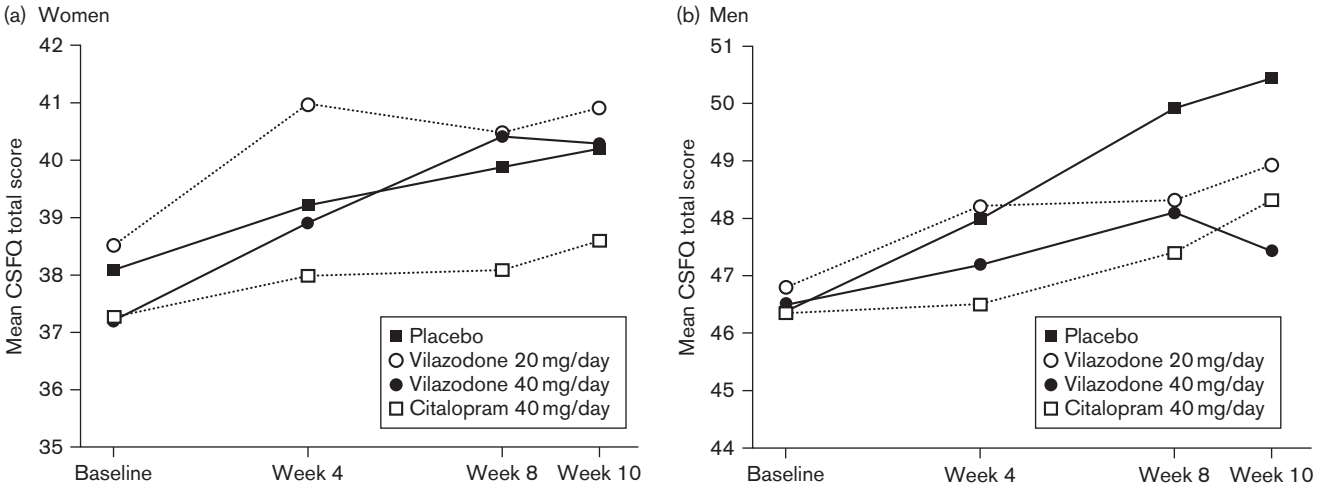
The number and percentage of adverse events (AEs) related to sexual function were reported by the preferred term for the safety population (all randomized patients who received at least one dose of double-blind treatment).

Table 1 Patient demographics and baseline CSFQ scores (CSFQ analysis population)

	Placebo ($n=264$)	Vilazodone 20 mg/day ($n=267$)	Vilazodone 40 mg/day ($n=259$)	Citalopram 40 mg/day ($n=257$)
Age [mean (SD)] (years)	42.0 (13.0)	42.1 (12.6)	41.0 (13.3)	42.9 (12.5)
Women (%)	55.7	56.9	57.1	57.6
White (%)	69.3	73.0	70.7	65.8
MADRS total score (mean)	31.2	31.4	31.1	31.2
CSFQ total score (mean)				
Women	38.1	38.5	37.2	37.3
Men	46.4	46.8	46.5	46.4
Sexual dysfunction (%)[a]				
Women	61.9	64.5	69.6	66.9
Men	50.4	53.9	55.0	52.3

CSFQ, Changes in Sexual Functioning Questionnaire; MADRS, Montgomery–Åsberg Depression Rating Scale.
[a]Sexual dysfunction at baseline was defined as CSFQ total score ≤41 (women) or ≤47 (men) (Clayton *et al.*, 1997).

Fig. 1



CSFQ scores by week in women (a) and men (b). CSFQ, Changes in Sexual Functioning Questionnaire.

Results

Patient demographics

The CSFQ analysis population comprised 1047 patients (Table 1). Baseline demographic characteristics were similar among treatment groups; mean baseline CSFQ total scores were ~38 for women and 46 for men. More than half of the patients had baseline sexual dysfunction, with prevalence higher for women than men, but similar across treatment groups.

CSFQ total score changes in women and men

In all treatment groups, CSFQ total score increased from baseline to week 10 for both women and men (Fig. 1). In women, mean change from baseline in CSFQ total score was 2.0 for placebo, 1.9 for vilazodone 20 mg/day, 3.0 for vilazodone 40 mg/day, and 1.2 for citalopram. In men, mean change from baseline was 3.5 for placebo, 2.4 for vilazodone 20 mg/day, 1.2 for vilazodone 40 mg/day, and 2.1 for citalopram.

CSFQ total score changes in MADRS responders and nonresponders

In the CSFQ analysis population, 50.4% of placebo patients, 64.1% of vilazodone 20 mg/day, 64.6% of vilazodone 40 mg/day, and 62.9% of citalopram patients met the criteria for MADRS response (≥50% improvement from baseline) at the end of double-blind treatment. For all treatment groups, MADRS responders and nonresponders had comparable baseline CSFQ total scores (Table 2). Overall, MADRS responders versus nonresponders had greater changes in CSFQ total scores; in male and female MADRS responders, CSFQ total score increased from baseline to week 10 across all treatment groups. In women, mean changes from baseline in CSFQ total score were greater in placebo-treatment and vilazodone-treatment groups versus citalopram; in men, CSFQ total score improvements were greater in placebo patients versus active treatment. In MADRS nonresponders, CSFQ total score changes were generally small; placebo-treated men had modest CSFQ total score

Table 2 Change from baseline to week 10 in CSFQ total scores in MADRS responders and nonresponders[a] (CSFQ analysis population)

MADRS response status	Placebo	Vilazodone 20 mg/day	Vilazodone 40 mg/day	Citalopram 40 mg/day
MADRS responders (≥50% improvement in MADRS)				
Women (*n*)	58	73	70	72
Baseline CSFQ score (mean)	38.8	39.3	37.7	38.6
CSFQ change from baseline (mean)	3.84	3.82	5.06	2.33
Men (*n*)	49	56	54	57
Baseline CSFQ score (mean)	48.6	47.4	47.3	47.2
CSFQ change from baseline (mean)	4.35	3.21	2.26	2.67
MADRS nonresponders				
Women (*n*)	60	41	38	50
Baseline CSFQ score (mean)	37.6	38.3	36.8	35.7
CSFQ change from baseline (mean)	0.27	−1.41	−0.87	−0.42
Men (*n*)	45	31	30	26
Baseline CSFQ score (mean)	45.0	44.9	44.3	44.3
CSFQ change from baseline (mean)	2.60	0.97	−0.80	0.77

CSFQ, Changes in Sexual Functioning Questionnaire; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale.
[a]Patients who met/did not meet response criteria (MADRS improvement ≥ 50%) at week 10 (LOCF).

Table 3 Change from baseline to week 10 in CSFQ total score in patients with and without baseline sexual dysfunction[a] (CSFQ analysis population)

Baseline sexual function status	Placebo	Vilazodone 20 mg/day	Vilazodone 40 mg/day	Citalopram 40 mg/day
Normal sexual function				
Women (*n*)	46	44	33	41
Baseline (mean)	47.7	47.7	47.5	47.3
CSFQ change from baseline (mean)	−1.09	−1.48	−0.55	−1.05
Men (*n*)	48	37	37	37
Baseline (mean)	54.0	54.2	54.2	53.7
CSFQ change from baseline (mean)	0.71	0.41	−0.95	0.32
Sexual dysfunction				
Women (*n*)	72	70	75	81
Baseline (mean)	32.0	33.5	32.9	32.4
CSFQ change from baseline (mean)	4.01	4.09	4.52	2.35
Men (*n*)	46	50	47	46
Baseline (mean)	39.4	40.8	40.0	40.3
CSFQ change from baseline (mean)	6.43	3.90	2.83	3.48

CSFQ, Changes in Sexual Functioning Questionnaire.
[a]Sexual dysfunction at baseline was defined as having CSFQ total score ≤ 41 (women) or ≤ 47 (men) (Clayton *et al.*, 1997).

increases and patients in active-treatment groups had small increases or decreases in CSFQ total score.

CSFQ total score changes by baseline sexual function

In patients with normal baseline sexual function, CSFQ total score changes from baseline to week 10 were generally small for all treatment groups (Table 3). Conversely, in patients with sexual dysfunction at baseline, CSFQ total scores improved from baseline to week 10 in all treatment groups. For women, improvements were largest in the placebo-treatment and vilazodone-treatment groups. For men, improvements were largest in the placebo group relative to the active-treatment groups; CSFQ improvements in active-treatment groups were comparable.

In women with baseline sexual dysfunction, 33 and 39% of patients taking vilazodone 20 and 40 mg/day, respectively, improved to normal sexual function during treatment; the shift to normal sexual function was slightly lower in the placebo (28%) and citalopram (27%) groups (Table 4). In women with normal baseline sexual function, ~80% maintained normal sexual function during treatment.

In men with baseline sexual dysfunction, improvement to normal sexual function occurred in ~40% of patients in the placebo, vilazodone 40 mg/day, and citalopram groups; in the vilazodone 20 mg/day group, 33% of patients shifted to normal sexual function (Table 4). For men with normal baseline sexual function, slightly more citalopram-treated than placebo-treated or vilazodone-treated patients met sexual dysfunction criteria during treatment.

CSFQ domain score changes by baseline sexual function

In patients with baseline sexual dysfunction, improvements were seen on every CSFQ domain (representing the different phases of the sexual cycle) for men and women in all treatment groups (Table 5). In patients with normal sexual function, CSFQ domain scores either minimally improved or decreased for all treatment groups.

Adverse events related to sexual function

In the overall safety population, spontaneously reported AEs related to sexual function were slightly more frequent in patients in the active-treatment groups than in

Table 4 Change in sexual function status during double-blind treatment (CSFQ analysis population)

Baseline sexual function[a]	Sexual function status during double-blind treatment[b]	Placebo (%)	Vilazodone 20 mg/day (%)	Vilazodone 40 mg/day (%)	Citalopram 40 mg/day (%)
Women					
Sexual dysfunction	Sexual dysfunction	72.5	66.7	60.7	72.7
	Normal sexual function	27.5	33.3	39.3	27.3
Normal sexual function	Sexual dysfunction	16.3	22.2	18.9	16.7
	Normal sexual function	83.7	77.8	81.1	83.3
Men					
Sexual dysfunction	Sexual dysfunction	58.8	66.7	60.8	62.0
	Normal sexual function	41.2	33.3	39.2	38.0
Normal sexual function	Sexual dysfunction	7.3	10.6	11.6	17.5
	Normal sexual function	92.7	89.4	88.4	82.5

CSFQ, Changes in Sexual Functioning Questionnaire.
[a]Sexual dysfunction at baseline was defined as CSFQ total score ≤41 (women) or ≤47(men) (Clayton *et al.*, 1997).
[b]Sexual dysfunction during double-blind treatment period was defined as CSFQ total score ≤41 (women) or ≤47 (men) for two consecutive visits during double-blind treatment.

Table 5 Mean change from baseline to week 10 in CSFQ domain scores (CSFQ analysis population)

CSFQ domain by baseline sexual function status	Placebo	Vilazodone 20 mg/day	Vilazodone 40 mg/day	Citalopram 40 mg/day
Pleasure				
Women				
Sexual dysfunction	0.57	0.56	0.61	0.31
Normal sexual function	0.09	−0.18	0.33	−0.20
Men				
Sexual dysfunction	0.87	0.72	0.43	0.41
Normal sexual function	0.19	0.27	0.14	0.35
Desire/frequency				
Women				
Sexual dysfunction	0.54	0.74	0.76	0.15
Normal sexual function	−0.28	−0.02	0.06	−0.29
Men				
Sexual dysfunction	0.80	0.54	0.43	0.48
Normal sexual function	0.23	0.00	−0.32	−0.05
Desire/interest				
Women				
Sexual dysfunction	0.86	0.81	0.55	0.63
Normal sexual function	0.13	−0.41	−0.61	0.41
Men				
Sexual dysfunction	1.50	1.24	0.87	0.65
Normal sexual function	0.15	0.30	0.11	0.46
Arousal				
Women				
Sexual dysfunction	1.11	1.01	1.20	0.80
Normal sexual function	−0.28	−0.02	0.15	−0.12
Men				
Sexual dysfunction	1.87	0.92	0.70	1.28
Normal sexual function	0.06	−0.11	−0.24	0.27
Orgasm				
Women				
Sexual dysfunction	0.75	0.97	1.21	0.21
Normal sexual function	−0.67	−0.73	−0.58	−1.00
Men				
Sexual dysfunction	1.39	0.48	0.53	0.59
Normal sexual function	0.08	0.16	−0.68	−0.62

CSFQ, Changes in Sexual Functioning Questionnaire.

the placebo group, and were most frequent in the citalopram group (Table 6), especially for anorgasmia and loss of libido. Incidence of libido decreased and erectile dysfunction (males) occurred with similar frequencies in the citalopram, vilazodone, and placebo groups. Discontinuation because of a sexual function-related AE occurred in one placebo patient (erectile dysfunction) and one citalopram patient (premature ejaculation). No vilazodone patient had a sexual function-related AE that resulted in study discontinuation.

Discussion and conclusion

Sexual dysfunction is both a common symptom of depression and an effect associated with serotonin reuptake inhibitor antidepressant treatments, including SSRI and serotonin norepinephrine reuptake inhibitor first-line treatment options (Kennedy and Rizvi, 2009). Improved sexual functioning during effective antidepressant treatment suggests that the positive effects of antidepressant treatment (symptom improvement) and the potential negative serotonergic effects of the medication may

Table 6 Incidence of adverse events related to sexual function (safety population)

	n (%)											
	Placebo ($n=281$)			Vilazodone 20 mg/day ($n=288$)			Vilazodone 40 mg/day ($n=287$)			Citalopram 40 mg/day ($n=282$)		
Preferred term[a]	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
Libido decreased	2 (1.6)	1 (0.6)	3 (1.1)	3 (2.5)	3 (1.8)	6 (2.1)	4 (3.3)	1 (0.6)	5 (1.7)	2 (1.7)	2 (1.2)	4 (1.4)
Loss of libido	0	0	0	0	0	0	0	0	0	2 (1.7)	1 (0.6)	3 (1.1)
Libido increased	0	0	0	1 (0.8)	0	1 (0.3)	0	0	0	0	0	0
Anorgasmia	0	0	0	0	1 (0.6)	1 (0.3)	1 (0.8)	0	1 (0.3)	2 (1.7)	2 (1.2)	4 (1.4)
Orgasm abnormal	0	0	0	2 (1.6)	0	2 (0.7)	0	0	0	1 (0.9)	0	1 (0.4)
Premature ejaculation	0	0	0	0	0	0	0	0	0	1 (0.9)	0	1 (0.9)
Erectile dysfunction	3 (2.4)	0	3 (2.4)	0	0	0	3 (2.4)	0	3 (2.4)	3 (2.6)	0	3 (2.6)
Ejaculation delayed	0	0	0	1 (0.8)	0	1 (0.8)	2 (1.6)	0	2 (1.6)	2 (1.7)	0	2 (1.7)
Sexual dysfunction	0	0	0	0	0	0	1 (0.8)	0	1 (0.3)	0	0	0
Ejaculation failure	0	0	0	0	0	0	0	0	0	1 (0.9)	0	1 (0.9)

AEs, adverse events.
[a]If more than one AE was coded to the same preferred term for a patient, the patient was counted only once for that preferred term. AEs were coded by the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1.

'equalize' to an extent where a patient can achieve both mood and sexual function benefits. Evaluating the patient factors (e.g. sex, baseline sexual function status) and treatment factors (e.g. response to treatment, antidepressant mechanism of action) that may be related to sexual function may enhance clinical management of MDD.

Approximately 55–60% of patients met the criteria for baseline sexual dysfunction in this study, with a higher percentage among women than men. This is similar to the level of baseline sexual dysfunction in the phase III vilazodone study that used the CSFQ (55–60%) (Khan *et al.*, 2011) and other studies that have evaluated sexual function in patients with untreated depression (Angst, 1998; Bonierbale *et al.*, 2003). In the prospectively defined protocol-specified analyses of the study, CSFQ changes from baseline indicated improvement in sexual functioning in all treatment groups, although differences versus placebo did not reach statistical significance (Mathews *et al.*, 2015). Of note, this study was not powered to detect statistical differences between groups in sexual functioning.

In post-hoc analyses, numerical improvements in CSFQ score from baseline to the end of the study occurred in all treatment subgroups; no inferential statistics were performed so the significance of the increases versus placebo could not be determined. In this 10-week study, increases in CSFQ scores were seen as early as week 4 in all patient subgroups except men treated with citalopram, where noticeable increases in CSFQ scores did not occur until week 8. For women, improvements in CSFQ scores were similar in the placebo-treatment and vilazodone-treatment groups and lower in the citalopram group. For men, improvements in CSFQ scores were similar between active-treatment groups and higher in the placebo group.

In patients who responded to antidepressant treatment (≥50% improvement from baseline in MADRS total scores), marked improvements in CSFQ total score (+2.26 to +5.06) were seen. CSFQ total score changes were greater in women than men for vilazodone patients, but greater in men than women for placebo and citalopram patients. Of note, as a three-point increase in CSFQ total score is considered clinically meaningful improvement, (Bobes *et al.*, 2002) change in sexual functioning exceeded this level for female responders in the vilazodone 20 and 40 mg/day groups and the placebo group, and for male responders in the vilazodone 20 mg/day and placebo groups. In patients on active treatment who did not meet MADRS response criteria, CSFQ total scores decreased or increased only modestly (-1.41 to +0.97). Placebo patients who did not meet MADRS response criteria had moderate increases in CSFQ total scores. These results were similar to those seen in a duloxetine study in which patients who remitted had improved sexual functioning, whereas those who did not remit had worsened sexual functioning (Clayton *et al.*, 2007). Of note, these results are somewhat dependent on the mechanism of action of SSRIs and serotonin norepinephrine reuptake inhibitors as antidepressants without significant negative effects on sexual functioning (e.g. bupropion or mirtazapine) do not strongly show this pattern; baseline sexual function is an additional factor.

Comparing the effects of antidepressant treatment in patients with normal sexual function and sexual dysfunction at baseline may allow for more discriminating evaluation of sexual dysfunction due to depression relative to sexual dysfunction because of the effects of antidepressant treatment. Improvement in CSFQ total scores for patients with baseline sexual dysfunction would presumably be associated with improvement in depression minus potential direct serotonergic adverse effects. CSFQ improvement in patients with normal baseline sexual function would not be expected; in this case, worsening of sexual function would primarily be because of direct adverse serotonergic antidepressant effects and, to a lesser extent, worsening of depression.

In these analyses, the effect of antidepressant treatment relative to sexual function at baseline appeared to be variable according to sex, treatment group, and the phase of the sexual cycle.

In women with sexual dysfunction at baseline, ~27% (placebo and citalopram) to 39% (vilazodone 40 mg/day) improved to normal sexual function in the course of treatment. The largest increases in CSFQ total scores, indicating improved sexual functioning, were in the placebo (4.01) and vilazodone 20 mg/day (4.09) and 40 mg/day (4.52) groups; these changes met the criteria for clinically meaningful improvement. Smaller, not clinically meaningful, improvements were seen in the citalopram group (2.35).

Analyzing changes by phases of the sexual cycle in women with baseline sexual dysfunction suggested that the largest improvements occurred in arousal for all treatment groups; improvements in sexual desire (both interest and frequency) were of lower magnitude and the smallest improvements occurred in the pleasure domain. These findings align with previous research suggesting that depression-related effects on sexual function usually occur through loss of libido and reduced desire and arousal (Clayton *et al.*, 2014); as such, improvement in depression symptoms may specifically ameliorate these problems.

Interestingly, marked improvements in orgasm for women with baseline sexual dysfunction were seen in the vilazodone groups but not in the citalopram group, which may be relevant to the different mechanisms of action in the two compounds. Orgasm and ejaculation dysfunction are not generally considered core sexual problems associated with MDD, but they are commonly associated with SSRI treatment (Clayton *et al.*, 2014). Cerebral serotonin (5-HT_{1A}) receptors are thought to play a role in mediating the ejaculatory response and the activity of vilazodone at the 5-HT_{1A} receptor may potentially attenuate the inhibitory effects of increased serotonin levels on orgasm/ejaculation (Giuliano and Clement, 2005).

In men with baseline sexual dysfunction, CSFQ total scores improved the most in the placebo group; increases in the vilazodone and citalopram groups were smaller and comparable. Relative to women, higher percentages of men across treatment groups improved from baseline sexual dysfunction to normal sexual function (33–41%) during antidepressant treatment. This may be generally because of higher mean CSFQ baseline scores for men relative to women as mean increase in CSFQ total scores was higher in women than men for all treatment groups except placebo.

For men with baseline sexual dysfunction in all treatment groups, the largest improvements occurred in the desire/interest and arousal phases of the sexual cycle. Improvement in orgasm was markedly higher in the placebo group versus the active-treatment groups, which may possibly be linked to adverse effects of increased serotonin activity on orgasm/ejaculation with serotonin reuptake inhibitors. It is unclear why women in the vilazodone groups had greater benefits in orgasm relative to men; antidepressant effects across the various phases of the sexual cycle may be sex dependent and more research in this area is warranted.

The percentage of women with normal baseline sexual function who met sexual dysfunction criteria during double-blind treatment was similar among treatment groups (16–22%). Moderate decreases in CSFQ total scores that were not considered clinically meaningful were seen across treatment groups (−1.48 to −0.55). For vilazodone patients, decreases in CSFQ scores appeared to be driven primarily by orgasm dysfunction and, to a lesser extent, by decreases in interest in sex. Orgasm dysfunction was also the phase of the sexual cycle most adversely affected in citalopram patients; lesser adverse effects on pleasure and frequency of desire for sex were observed.

The observation that orgasm dysfunction was the major sexual side effect of vilazodone and citalopram is not surprising as previous studies have suggested that this is specifically mediated by SSRI treatment (Kennedy and Rizvi, 2009). Decrease in CSFQ orgasm scores was greater in the citalopram group relative to the vilazodone groups, which had decreases similar to placebo; this may again be because of 5-HT_{1A} partial agonist activity in vilazodone and the possibility that it may attenuate the effects of increased serotonin activity on orgasm/ejaculation inhibition.

In men with normal baseline sexual function, mean changes in CSFQ total scores were variable across treatment groups; small increases were observed in the placebo, vilazodone 20 mg/day, and citalopram groups, whereas decreases were seen in the vilazodone 40 mg/day group. Shifts from normal sexual function to sexual dysfunction were lower in the placebo (7%) and vilazodone 20 and 40 mg/day (11 and 12%, respectively) groups relative to the citalopram group (18%). In the vilazodone 40 mg/day and citalopram groups, the orgasm phase of the sexual cycle worsened the most; for the vilazodone 20 mg/day and the placebo groups, changes in all phases of the sexual cycle per CSFQ scores were small.

Overall, spontaneous reports of sexual function-related AEs were slightly more frequent with active-treatment groups than placebo, and were the most frequent with citalopram. Increased AE incidence in the citalopram group relative to placebo was most evident for anorgasmia, loss of libido, and ejaculation delayed. For vilazodone, orgasm abnormal and ejaculation delayed were increased relative to placebo. Libido decrease occurred in male and female patients across treatment groups. Sexual function-related AEs tended to align with the phases of the sexual cycle that worsened in patients with normal baseline sexual functioning.

Strengths of these analyses include the presence of the active control citalopram, which made it possible to observe sexual functioning effects in antidepressants with different mechanisms of action. The protocol-specified inclusion of the CSFQ, a validated assessment tool, allowed for detailed analyses of sexual function during antidepressant treatment, although the post-hoc analyses presented here were not prospectively defined in the study protocol. However, the trial was not specifically powered to detect between-group differences in changes in sexual function, which may explain the lack of statistical separation between citalopram and placebo on mean change from baseline to week 10 in CSFQ total score. In addition, the high MADRS placebo response rate may have also limited the ability to detect differences between citalopram and placebo on CSFQ assessments. Inclusion and exclusion criteria limit the generalizability of study results and the acute duration of treatment may be too short to fully evaluate sexual functioning. Additional limitations of these analyses include the lack inferential statistics, inability to make direct comparisons regarding sexual function because of small statistical power, and inability to identify the proportion of sexual dysfunction due to depression relative to the direct serotonergic effects of vilazodone and citalopram. Additional studies in larger patient populations, with specific emphasis on patients who are sexually active and have sexual dysfunction at baseline, are warranted so the effects of vilazodone on sexual function relative to other antidepressants can be more fully evaluated.

In all treatment groups, sexual function improved from baseline to the end of treatment in women and men subgroups, in MADRS responders, and in patients with baseline sexual dysfunction. In patients with baseline sexual dysfunction, all phases of the sexual cycle were improved for men and women in all treatment groups; in patients with normal sexual function, CSFQ domain scores minimally improved or decreased for all treatment groups. These findings suggest that improved sexual function may be associated with improvement of depressive symptoms, which may outweigh potential direct negative serotonergic effects of antidepressants in patients with MDD.

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Conflicts of interest

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