

Characterizing sexual function in patients with generalized anxiety disorder: a pooled analysis of three vilazodone studies

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Background: Vilazodone has been shown to reduce core symptoms of generalized anxiety disorder (GAD) in three randomized, double-blind, placebo-controlled trials. Since sexual dysfunction (SD) is not well characterized in GAD, a post hoc analysis of these trials was conducted to evaluate the effects of vilazodone on sexual functioning in GAD patients.

Materials and methods: Data were pooled from one fixed-dose trial of vilazodone 20 and 40 mg/day (NCT01629966) and two flexible-dose studies of vilazodone 20–40 mg/day (NCT01766401, NCT01844115) in adults with GAD. Sexual functioning was assessed using the Changes in Sexual Functioning Questionnaire (CSFQ). Outcomes included mean change from baseline to end of treatment (EOT) in CSFQ total score and percentage of patients shifting from SD at baseline (CSFQ total score ≤ 47 for males, ≤ 41 for females) to normal functioning at EOT. Treatment-emergent adverse events related to sexual functioning were also analyzed.

Results: A total of 1,373 patients were included in the analyses. SD at baseline was more common in females (placebo, 46.4%; vilazodone, 49%) than in males (placebo, 35.1%; vilazodone, 40.9%). CSFQ total score improvement was found in both females (placebo, +1.2; vilazodone, +1.6) and males (placebo, +2.1; vilazodone, +1.0), with no statistically significant differences between treatment groups. The percentage of patients who shifted from SD at baseline to normal sexual functioning at EOT was higher in males (placebo, 40.6%; vilazodone, 35.7%) than in females (placebo, 24.9%; vilazodone, 34.9%); no statistical testing was performed. Except for erectile dysfunction and delayed ejaculation in vilazodone-treated males (2.4% and 2.1%, respectively), no treatment-emergent adverse events related to sexual functioning occurred in $\geq 2\%$ of patients in either treatment group.

Conclusion: Approximately 35%–50% of patients in the vilazodone GAD studies had SD at baseline. Vilazodone and placebo had similar effects on CSFQ outcomes in both females and males, indicating a limited adverse impact on sexual functioning with vilazodone.

Keywords: vilazodone, generalized anxiety disorder, sexual dysfunction, clinical trials, post hoc analysis

Introduction

Sexual complaints are a common problem in the US general population, with prevalence estimated at 31% in males and 43% in females.¹ These complaints are even more common in psychiatric illnesses. Sexual dysfunction (SD) has been reported in 40%–65% of patients with major depressive disorder (MDD).² The relationship between SD and MDD is bidirectional, with SD increasing the risk of depression and vice versa.³ Complicating this clinical scenario are the unwanted sexual effects of serotonergic agents commonly used to treat depression and anxiety disorders. Approximately 35%–45%



of antidepressant-treated patients experience global SD, with 60%–80% of patients reporting decreased functioning in a specific phase of the sexual cycle.⁴

Among MDD patients, a population in which SD has been fairly well characterized,^{5–10} decreased desire, erectile difficulties, and delayed ejaculation are commonly reported in males; decreased desire, diminished arousal, and difficulty achieving orgasm are often reported in females. Comorbid depressive and anxiety disorders are often seen in clinical settings, and like depression symptoms, anxiety can be a prominent factor in the etiology of SD.¹¹ This is an important point to consider, since the estimated 12-month prevalence of anxiety disorders in the general population is 18% and the estimated lifetime prevalence is 29%.^{12,13} Although SD has been researched in some anxiety-related disorders (eg, social phobia, obsessive–compulsive disorder, posttraumatic stress disorder),² less is known about SD in patients with generalized anxiety disorder (GAD). One study, however, has shown SD to be present in 64% of GAD patients,¹⁴ which the investigators defined as a total score ≥ 17 or any item score ≥ 5 on the Arizona Sexual Experience Scale.¹⁵ This result was lower than the incidence of SD found in MDD patients (76%), but higher than was found in obsessive–compulsive disorder patients (50%).¹⁴

Vilazodone is a selective serotonin-reuptake inhibitor and 5-HT_{1A}-receptor partial agonist that is approved by the US Food and Drug Administration for the treatment of MDD in adults at the recommended dose of 20–40 mg/day.^{15,16} Based on findings from preclinical studies,¹⁶ it has been hypothesized that activation of 5-HT_{1A} receptors may offset the negative effects of increased serotonin action on sexual functioning. This hypothesis was consistent with results of a post hoc analysis of Arizona Sexual Experience Scale and Changes in Sexual Functioning Questionnaire (CSFQ)¹⁷ data from three vilazodone studies in adult MDD patients, which included two double-blind and placebo-controlled trials^{18,19} and a 52-week open-label extension study.²⁰ Results of this post hoc analysis indicated that vilazodone had a low adverse impact on sexual function in patients with MDD.⁸

Since vilazodone had shown anxiolytic effects in rats,²¹ and the 5-HT_{1A} mechanism of vilazodone is also found in anti-anxiety medications, such as buspirone, vilazodone was subsequently investigated for the treatment of adults with GAD in three double-blind, randomized, placebo-controlled trials. Based on the primary end point, defined as change from baseline in the Hamilton Anxiety Rating Scale (HAM-A),²² positive results with vilazodone versus placebo were reported in two flexible-dose trials (20–40 mg/day).^{23,24} In a fixed-dose

trial of vilazodone 20 or 40 mg/day, a statistically significant difference from placebo in HAM-A total score change was found with the higher vilazodone dose, but not the lower dose.²⁵ The CSFQ was included as a safety measure in all the three GAD studies. In the individual studies, small and similar mean changes in CSFQ total score were seen in both vilazodone- and placebo-treatment groups, suggesting similar effects of treatment on sexual functioning in adults with GAD. Pooled CSFQ data from these trials were analyzed post hoc to further evaluate the effects of treatment on SD and better characterize SD in adults with GAD.

Materials and methods

Study design and patients

Post hoc analyses were conducted using data from the three positive 8-week clinical trials of vilazodone in adult patients with GAD (NCT01766401,²³ NCT01844115,²⁴ and NCT01629966²⁵). All vilazodone-dose groups were pooled for this analysis.

Detailed methods for the individual studies have previously been reported.^{23–25} In brief, they included patients 18–70 years of age who met *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition – text revision criteria for GAD. At baseline, patients were required to have a HAM-A total score ≥ 20 , with scores ≥ 2 on HAM-A items 1 (anxious mood) and 2 (tension), Clinical Global Impression – Severity²⁶ score ≥ 4 (indicating at least moderate illness), and 17-item Hamilton Depression Rating Scale (HAM-D₁₇)²⁷ total score ≤ 17 . Typical exclusion criteria were applied, and included the following: an Axis I diagnosis other than GAD, nonresponse to adequate treatment trials of two or more selective serotonin-reuptake inhibitors or serotonin norepinephrine-reuptake inhibitors for GAD (≥ 8 weeks at the recommended dose), and suicide risk (past year attempt, score ≥ 3 on item 3 of the HAM-D₁₇, or investigator judgment).

In the constituent studies, prospective assessment of sexual functioning was conducted at week 0 (baseline), 4, and 8 using the CSFQ, a self-report 14-item questionnaire that evaluates the effects of antidepressant treatment on five domains of sexual functioning: pleasure, desire/frequency, desire/interest, arousal/erection (males) or arousal/excitement (females), and orgasm/ejaculation (males) or orgasm/completion (females) (Figure 1).²⁸ Global SD is defined as a CSFQ total score of ≤ 47 in males and ≤ 41 in females. SD in the CSFQ domains is defined using the following threshold scores: pleasure (≤ 4), desire/frequency (males ≤ 8 , females ≤ 6), desire/interest (males ≤ 11 , females ≤ 9), arousal/erection (≤ 13) or arousal/

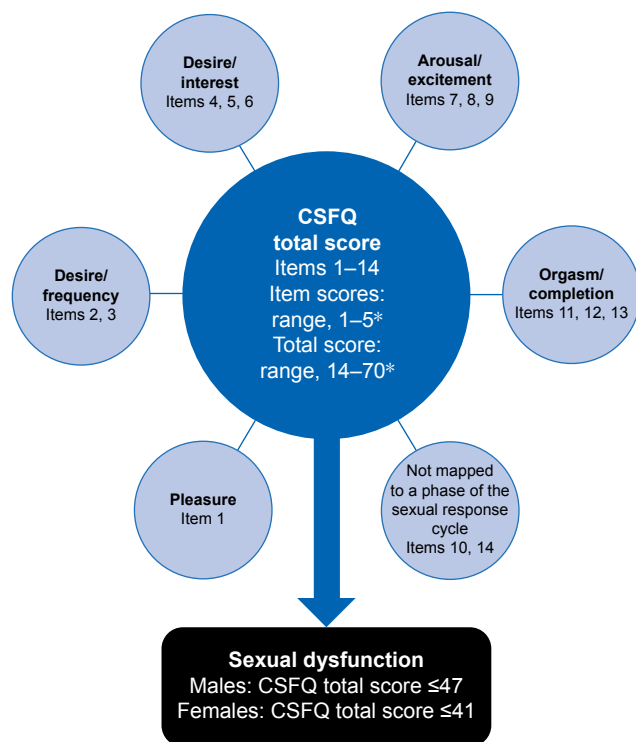


Figure 1 Items, domains, and scoring for the Changes in Sexual Functioning Questionnaire (CSFQ).

Note: *Lower scores indicate worse sexual functioning.

excitement (≤ 12), and orgasm/ejaculation (≤ 13) or orgasm/completion (≤ 11).

Screening, enrollment, and randomization of patients were independent of any measure or assessment of sexual functioning. No evaluations of sexual function status were performed before the baseline visit.

Post hoc analyses

Analyses were conducted in the pooled CSFQ-analysis population, defined as all randomized patients who took one or more doses of double-blind study drug and had a baseline and one or more available postbaseline CSFQ assessments. Each CSFQ-based analysis was conducted in patients from the CSFQ-analysis population who had available assessments that were appropriate for that analysis. For treatment-emergent adverse events (TEAEs) that were related to sexual functioning, analyses were conducted in the pooled safety population, defined as all randomized patients who had received one or more doses of the double-blind study drug.

The effects of treatment on sexual function were evaluated based on least squares mean (LSM) change from baseline to week 8 in CSFQ total score in all males and females, as well as in males and females categorized by age (≤ 50 or > 50 years), baseline sexual functioning status (with or

without SD), and HAM-A response. The LSM change from baseline to week 8 in CSFQ domain scores was also analyzed in all males and females included in the CSFQ-analysis population, as well as in males and females categorized by age. Least squares mean differences (LSMDs) between treatment groups and *P*-values for CSFQ total and domain-score changes were analyzed using a mixed-effect model for repeated measures, with treatment group, pooled study center, sex, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline-value-by-visit interaction as covariates.

The percentage of patients whose sexual functioning changed from SD status at baseline (ie, CSFQ total score of ≤ 47 in males and ≤ 41 in females) to normal functioning (ie, CSFQ total score ≥ 48 in males and ≥ 42 in females) at the end of double-blind treatment were analyzed descriptively. Descriptive statistics were also used to analyze the percentage of patients who shifted from normal sexual functioning at baseline to SD status at end of treatment. The incidence of TEAEs related to the sexual function in the pooled safety population was analyzed descriptively.

Results

Patient characteristics

The pooled CSFQ-analysis population consisted of 1,373 patients (placebo, $n=577$; vilazodone, $n=796$). Demographic characteristics were similar between treatment groups (Table 1). In the placebo and vilazodone groups, baseline SD was seen in 35% and 40.9% of males and 46.4% and 49% of females, respectively (Table 2). Mean baseline CSFQ total scores were lower in females than in males.

CSFQ total score changes

For change in baseline to week 8 in CSFQ total score, no significant differences between vilazodone and placebo were detected in males of any age, males categorized by age

Table 1 Patient demographics (CSFQ-analysis population)

Characteristics	Placebo ($n=577$)	Vilazodone 20–40 mg/day ($n=796$)
Age, years, mean (SDEV)	40.5 (13.4)	40.1 (13.3)
Females, n (%)	380 (65.9)	526 (66.1)
Males, n (%)	197 (34.1)	270 (33.9)
White, n (%)	456 (79)	613 (77)
Duration of GAD, years, mean (SDEV)	13.3 (12.3)	13.3 (12.6)
Age at GAD onset, years, mean (SDEV)	27.3 (14.3)	26.8 (14.1)
Previous treatment for GAD, n (%)	81 (14)	124 (15.6)

Abbreviations: CSFQ, Changes in Sexual Functioning Questionnaire; GAD, generalized anxiety disorder; SDEV, standard deviation.

Table 2 Baseline sexual functioning characteristics (CSFQ-analysis population)

Characteristics	n ^a	Placebo	n ^a	Vilazodone 20–40 mg/day
Females with sexual dysfunction, n (%) ^b	366	170 (46.4)	467	229 (49)
Males with sexual dysfunction, n (%) ^b	191	67 (35.1)	252	103 (40.9)
Baseline CSFQ total score, mean (SDEV)				
All patients	557	45 (10.2)	719	44.3 (9.98)
All females	366	42.3 (9.87)	467	41.7 (9.86)
Females without sexual dysfunction ^b	196	49.9 (5.74)	238	49.5 (5.76)
Females with sexual dysfunction ^b	170	33.6 (5.49)	229	33.6 (5.95)
All males	191	50.2 (8.74)	252	49.1 (8.32)
Males without sexual dysfunction ^b	124	55.2 (5.45)	149	54.5 (4.78)
Males with sexual dysfunction ^b	67	40.8 (5.37)	103	41.1 (5.51)

Notes: ^aPatients with available CSFQ assessments at baseline and at one or more postbaseline study visit (week 4 and/or week 8); ^bsexual dysfunction defined as CSFQ total score ≤ 47 in males and ≤ 41 in females.

Abbreviations: CSFQ, Changes in Sexual Functioning Questionnaire; SDEV, standard deviation.

(≤ 50 or > 50 years), females of any age, or females categorized by age (≤ 50 or > 50 years) (Table 3). LSMDs for CFSQ total score change in younger and older males (-0.9 and -1.1 , respectively; both $P > 0.05$) were similar to the LSMD found in all males (-1.1 ; $P = 0.0705$). LSMDs in younger and older females (0.4 and 0.3 , respectively; both $P > 0.05$) were also similar to the LSMD found in all females (0.4 ; $P = 0.3746$).

Among males and females with SD at baseline, mean improvements in CSFQ total scores were found with both vilazodone and placebo (Figure 2A), with no statistically significant differences between treatment groups at weeks 4 or 8. Among patients without SD at baseline, small decreases (< 1.5 points) in mean CSFQ total scores were seen in all patient groups, except for a slight increase (< 0.5 points) in placebo-treated males (Figure 2B). At week 4, in males and females without SD at baseline, the mean decrease in CSFQ total score was significantly greater in the vilazodone group compared with the placebo group; however, the difference between treatment groups was not significant at week 8.

The percentage of patients with a HAM-A response was 39.7% (229 of 557) for placebo and 48.6% (387 of 796) for vilazodone. In HAM-A responders at week 8, mean improvements in CSFQ total score were found with both placebo (males, $+2.6$; females, $+2.7$) and vilazodone (males, $+1.7$; females, $+3$) (Figure 3), with no significant differences between treatment groups in either males or females.

CSFQ domain-score changes

In males and females from both treatment groups, mean baseline scores were lower than SD thresholds in each of the five CSFQ domains (Table 3). Older males and females (> 50 years) had lower mean baseline scores across the CSFQ domains than younger patients (≤ 50 years), suggesting worse baseline sexual function in the older subgroups.

After 8 weeks of double-blind treatment, mean CSFQ domain scores generally remained above the score cutoff for SD (ie, no SD) in males and females from both treatment groups. In older males, a small mean worsening with vilazodone was found in desire/frequency, desire/interest, and orgasm/ejaculation (LSM change -0.0 , -0.1 , and -0.0 points, respectively). However, no statistically significant difference between vilazodone and placebo was found in any CSFQ domain in older or younger males. Older and younger females had mean improvements with both placebo and vilazodone in all CSFQ domains, with no statistically significant differences between treatment groups in any domain.

Changes in sexual function status

In both treatment groups, $> 80\%$ of males and females who had normal sexual function at baseline maintained their normal status until the end of double-blind treatment (Table 4). In both males and females with SD at baseline, approximately one-third of vilazodone-treated patients improved to normal sexual function status at the end of double-blind treatment. In males with baseline SD, the percentage of patients improving to normal function was lower with vilazodone (35.7%) than placebo (40.6%). However, in females with baseline SD, the percentage of patients improving to normal function was greater with vilazodone (34.9%) than with placebo (24.9%). No statistical testing between treatment groups was conducted for any of these outcomes.

Adverse events related to sexual function

In the pooled safety population (placebo, $n = 621$; vilazodone, $n = 854$), TEAEs related to sexual function were more common with vilazodone than with placebo (Table 5). Decreased libido was the most common sexual function TEAE in the overall population and in vilazodone-treated female patients; eight male patients (four in each treatment

Table 3 CSFQ total and domain score changes in males and females (CSFQ-analysis population)

CSFQ score (range) ^a	Placebo			Vilazodone 20–40 mg/day			LSMD (95% CI)	P-value
	n ^b	Mean BL (SDEV)	LSM change from BL (SE)	n ^b	Mean BL (SDEV)	LSM change from BL (SE)		
All males								
Total (14–70)	174	50 (8.7)	2.1 (0.49)	226	49.2 (8.32)	1.0 (0.43)	–1.1 (–2.31 to 0.9)	0.0705
Pleasure (1–5)	174	2.9 (1.13)	0.5 (0.07)	226	2.7 (1.03)	0.5 (0.07)	–0.0 (–0.21 to 0.15)	0.7324
Desire/frequency (2–10)	174	6.7 (1.74)	0.2 (0.11)	226	6.4 (1.8)	0.1 (0.1)	–0.1 (–0.42 to 0.14)	0.3173
Desire/interest (3–15)	174	9.0 (2.67)	0.5 (0.15)	226	9.3 (2.36)	0.2 (0.13)	–0.3 (–0.7 to 0.01)	0.056
Arousal/erection (3–15)	174	10.8 (2.75)	0.5 (0.16)	226	10.5 (2.73)	0.3 (0.14)	–0.2 (–0.53 to 0.22)	0.4235
Orgasm/ejaculation (3–15)	174	11 (2.57)	0.4 (0.15)	226	10.6 (2.4)	0.1 (0.13)	–0.3 (–0.66 to 0.08)	0.1286
Males ≤50 years								
Total (14–70)	130	50.8 (8.77)	2.3 (0.56)	164	50.6 (7.95)	1.3 (0.59)	–0.9 (–2.3 to 0.43)	0.1781
Pleasure (1–5)	130	3 (1.1)	0.5 (0.09)	164	2.8 (1.01)	0.5 (0.08)	–0.0 (–0.23 to 0.22)	0.9719
Desire/frequency (2–10)	130	6.9 (1.73)	0.3 (0.13)	164	6.7 (2.43)	0.1 (0.12)	–0.2 (–0.49 to 0.16)	0.3239
Desire/interest (3–15)	130	9 (2.72)	0.6 (0.17)	164	9.4 (2.43)	0.3 (0.15)	–0.4 (–0.78 to 0.06)	0.0961
Arousal/erection (3–15)	130	11 (2.72)	0.5 (0.18)	164	11 (2.54)	0.3 (0.16)	–0.2 (–0.64 to 0.23)	0.3546
Orgasm/ejaculation (3–15)	130	11.2 (2.53)	0.4 (0.17)	164	11 (2.37)	0.2 (0.15)	–0.2 (–0.65 to 0.19)	0.283
Males >50 years								
Total (14–70)	44	47.6 (8.12)	1.8 (1.05)	62	45.3 (8.06)	0.7 (0.86)	–1.1 (–3.81 to 1.54)	0.4017
Pleasure (1–5)	44	2.5 (1.15)	0.5 (0.12)	62	2.3 (1.01)	0.4 (0.1)	–0.1 (–0.4 to 0.23)	0.5784
Desire/frequency (2–10)	44	6.2 (1.72)	0.2 (0.23)	62	5.6 (1.68)	–0.0 (0.19)	–0.2 (–0.79 to 0.36)	0.463
Desire/interest (3–15)	44	8.8 (2.55)	0.4 (0.29)	62	8.9 (2.14)	–0.1 (0.24)	–0.5 (–1.21 to 0.27)	0.2083
Arousal/erection (3–15)	44	10 (2.76)	0.5 (0.35)	62	9.2 (2.81)	0.5 (0.29)	–0.0 (–0.91 to 0.87)	0.9584
Orgasm/ejaculation (3–15)	44	10.3 (2.56)	0.3 (0.35)	62	9.5 (2.16)	–0.0 (0.29)	–0.4 (–1.27 to 0.52)	0.4086
All females								
Total (14–70)	337	42.1 (9.89)	1.2 (0.37)	408	41.9 (9.87)	1.6 (0.35)	0.4 (–0.52 to 1.39)	0.3746
Pleasure (1–5)	339	2.5 (1.21)	0.3 (0.05)	408	2.5 (1.17)	0.4 (0.05)	0.1 (–0.06 to 0.21)	0.2791
Desire/frequency (2–10)	339	5.3 (1.78)	0.2 (0.08)	409	5.3 (1.81)	0.2 (0.07)	–0.0 (–0.19 to 0.19)	0.9844
Desire/interest (3–15)	339	7.3 (2.52)	0.2 (0.11)	409	7.3 (2.5)	0.2 (0.1)	–0.0 (–0.3 to 0.23)	0.8189
Arousal/excitement (3–15)	338	8.7 (2.74)	0.4 (0.11)	408	8.6 (2.75)	0.6 (0.1)	0.1 (–0.13 to 0.43)	0.3008
Orgasm/completion (3–15)	337	9.8 (3.2)	0.3 (0.13)	408	9.6 (3.46)	0.3 (0.12)	–0.0 (–0.32 to 0.34)	0.9434
Females ≤50 years								
Total (14–70)	238	43.7 (9.46)	1.3 (0.45)	304	43.3 (9.59)	1.6 (0.4)	0.4 (–0.74 to 1.45)	0.5249
Pleasure (1–5)	238	2.7 (1.18)	0.3 (0.06)	304	2.7 (1.15)	0.4 (0.06)	0.1 (–0.03 to 0.28)	0.1255
Desire/frequency (2–10)	238	5.6 (1.69)	0.1 (0.09)	305	5.6 (1.77)	0.2 (0.08)	0.0 (–0.21 to 0.24)	0.8907
Desire/interest (3–15)	238	7.6 (2.53)	0.2 (0.13)	305	7.5 (2.5)	0.2 (0.11)	–0.0 (–0.33 to 0.3)	0.9271
Arousal/excitement (3–15)	238	9.2 (2.55)	0.4 (0.13)	304	9.0 (2.67)	0.5 (0.12)	0.1 (–0.21 to 0.45)	0.4849
Orgasm/completion (3–15)	238	10.1 (2.97)	0.2 (0.15)	304	10 (3.34)	0.2 (0.13)	–0.0 (–0.35 to 0.36)	0.9832
Females >50 years								
Total (14–70)	99	38.3 (9.9)	2 (0.74)	104	37.6 (9.49)	2.3 (0.72)	0.3 (–1.63 to 2.24)	0.7543
Pleasure (1–5)	101	2.1 (1.17)	0.4 (0.1)	104	2 (1.07)	0.3 (0.1)	–0.1 (–0.31 to 0.2)	0.6876
Desire/frequency (2–10)	101	4.4 (1.68)	0.4 (0.13)	104	4.4 (1.58)	0.4 (0.13)	–0.0 (–0.38 to 0.29)	0.8049
Desire/interest (3–15)	101	6.6 (2.34)	0.3 (0.2)	104	6.5 (2.36)	0.3 (0.2)	–0.0 (–0.54 to 0.52)	0.9781
Arousal/excitement (3–15)	100	7.5 (2.83)	0.4 (0.22)	104	7.3 (2.62)	0.7 (0.21)	0.2 (–0.31 to 0.81)	0.3842
Orgasm/completion (3–15)	99	9 (3.57)	0.4 (0.29)	104	8.7 (3.65)	0 (0.28)	0.0 (–0.75 to 0.78)	0.9668

Notes: ^aHigher CSFQ scores indicate better sexual functioning. CSFQ scores indicating sexual dysfunction: total (males ≤47, females ≤41), pleasure (≤4), desire/frequency (males ≤8, females ≤6), desire/interest (males ≤11, females ≤9), arousal/erection or arousal/excitement (males ≤13, females ≤12), and orgasm/ejaculation or orgasm/completion (males ≤13, females ≤11). ^bSubjects (males or females) with an available CSFQ assessment at both baseline and week 8.

Abbreviations: BL, baseline; CSFQ, Changes in Sexual Functioning Questionnaire; LSM, least squares mean; LSMD, least squares mean difference; SDEV, standard deviation; SE, standard error; CI, confidence interval.

group) also reported a decrease in libido. The most common sexual function TEAEs for vilazodone-treated males were erectile dysfunction (2.4%) and delayed ejaculation (2.1%). No other sexual function TEAE occurred in >2% of patients in either treatment group.

Discussion

The results of this post hoc analysis, conducted using data pooled from three randomized and placebo-controlled trials of vilazodone 20–40 mg/day, indicated that vilazodone had similar effects to placebo on sexual functioning in adults with GAD.

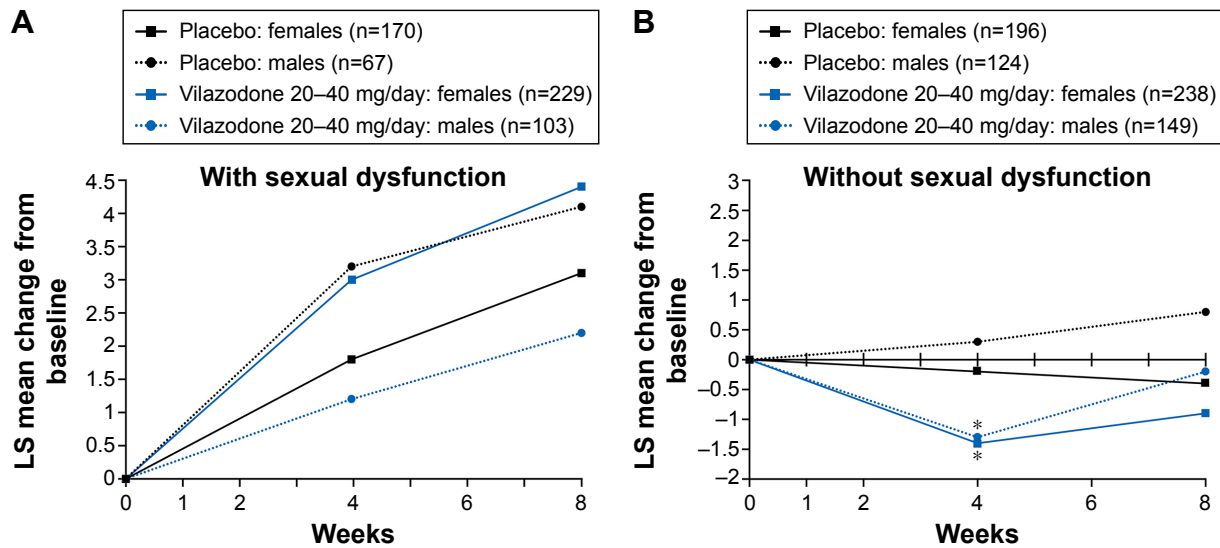


Figure 2 CSFQ total score change from baseline to week 8 in patients with (A) or without (B) baseline sexual dysfunction (CSFQ-analysis population).

Note: Sexual dysfunction defined as CSFQ total score ≤ 47 (males) or ≤ 41 (females).
Abbreviations: CSFQ, Changes in Sexual Functioning Questionnaire; LS, least squares.

In male and female patients, mean changes in CSFQ total and domain scores from baseline to end of double-blind treatment were small in both treatment groups, with no statistically significant differences between vilazodone and placebo. When analyzed by age-groups, no significant differences were found in older patients (males and females > 50 years) or younger patients (males and females ≤ 50 years). These findings were not unexpected, since a previous post hoc analysis in adult MDD patients also showed vilazodone to have minimal impact on sexual functioning.⁸

One aim of this post hoc analysis was to characterize SD in GAD, since little is known in this area, especially compared to MDD. At baseline, global SD (CSFQ total score ≤ 47 for males

or ≤ 41 for females) was found in both treatment groups, with a higher percentage in females (placebo, 46.4%; vilazodone, 49%) than in males (placebo, 35.1%; vilazodone, 40.9%). Consistent with a previous report of SD in GAD patients,¹⁴ these incidences of SD in vilazodone GAD studies were lower than the results from MDD vilazodone studies (68% of females, 50% of males).⁸ Nonetheless, the number of GAD patients with baseline SD in this report represents a sizable portion of the overall pooled GAD study population.

Deficits in different phases of the sexual functioning cycle may vary across psychiatric disorders. Decreased libido is the most commonly reported problem in depressed patients,

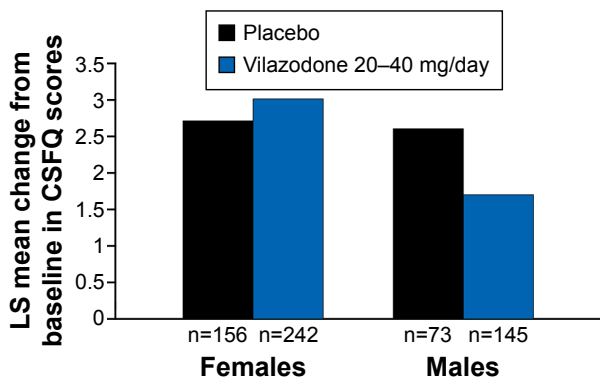


Figure 3 CSFQ total score change from baseline to week 8 in patients with HAM-A response (CSFQ-analysis population).

Note: Response defined as $\geq 50\%$ improvement from baseline in HAM-A total score.

Abbreviations: CSFQ, Changes in Sexual Functioning Questionnaire; HAM-A, Hamilton Anxiety Rating Scale; LS, least squares.

Table 4 Changes in sexual function status during DB treatment (CSFQ-analysis population)

Sexual functioning status at baseline ^a	Sexual functioning status at end of DB treatment ^a	Placebo, %	Vilazodone 20–40 mg/day, %
Females			
Dysfunction	Dysfunction	75.1	65.1
Dysfunction	Normal function	24.9	34.9
Normal function	Dysfunction	10.3	17.9
Normal function	Normal function	89.7	82.1
Males			
Dysfunction	Dysfunction	59.4	64.3
Dysfunction	Normal function	40.6	35.7
Normal function	Dysfunction	6.3	11.4
Normal function	Normal function	93.8	88.6

Note: ^aSexual dysfunction defined as CSFQ total score ≤ 47 in males and ≤ 41 in females; normal function designates patients who do not meet the sexual dysfunction criteria.

Abbreviations: CSFQ, Changes in Sexual Functioning Questionnaire; DB, double-blind.

Table 5 Sexual function adverse events (safety population)

	Placebo			Vilazodone 20–40 mg/day		
	Overall (n=621)	Males (n=210)	Females (n=411)	Overall (n=854)	Males (n=291)	Females (n=563)
Patients with ≥ 1 TEAE ^a related to sexual function, n (%)	8 (1.3)	8 (3.8)	0	39 (4.6)	27 (9.3)	12 (2.1)
TEAEs related to sexual function, n (%)						
Libido decreased	4 (0.6)	4 (1.9)	0	14 (1.6)	4 (1.4)	10 (1.8)
Anorgasmia	0	0	0	7 (0.8)	4 (1.4)	3 (0.5)
Erectile dysfunction ^b	1 (0.5)	1 (0.5)	0	7 (2.4)	7 (2.4)	0
Ejaculation delayed ^b	2 (1)	2 (1)	0	6 (2.1)	6 (2.1)	0
Orgasm abnormal	1 (0.2)	1 (0.5)	0	5 (0.6)	4 (1.4)	1 (0.2)
Disturbance in sexual arousal	0	0	0	1 (0.1)	0	1 (0.2)
Ejaculation disorder ^b	0	0	0	1 (0.3)	1 (0.3)	0
Loss of libido	0	0	0	1 (0.1)	1 (0.3)	0
Premature ejaculation ^b	0	0	0	1 (0.3)	1 (0.3)	0
Sexual dysfunction	1 (0.2)	1 (0.5)	0	1 (0.1)	1 (0.3)	0
Testicular pain ^b	0	0	0	1 (0.3)	1 (0.3)	0

Notes: ^aVersion 16.1 of MedDRA used to code AEs; ^bpercentage based on the number of male patients in the pooled safety population (placebo, n=210; vilazodone, n=291).

Abbreviations: AEs, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

although problems with arousal, erectile dysfunction, and absent or delayed orgasm are also prevalent.²⁹ In social phobia, SD may be related to performance anxiety, with premature ejaculation and impaired sexual satisfaction seen in males and impaired arousal, desire, activity, and satisfaction noted in females^{30–33} High levels of sexual aversion and phobic avoidance have been noted in patients with panic disorder and obsessive–compulsive disorder,^{11,34} while erectile dysfunction and premature ejaculation have been reported in combat veterans with posttraumatic stress disorder.³⁵ In the current post hoc analysis, mean scores at baseline were lower than SD thresholds for all CSFQ domains in both males and females, which largely explains the high levels of global SD seen in the vilazodone GAD studies.

Since sexual functioning can be negatively affected by age-related medical conditions, such as menopause, hypertension, benign prostatic hyperplasia, heart disease, and type 2 diabetes,^{36–39} analyses were conducted in male and female patients categorized by age (≤ 50 or >50 years). In comparison to younger females, older females in both treatment groups had lower mean CFSQ total and domain scores at baseline; in both age groups, mean baseline CSFQ scores were lower than SD thresholds. These findings suggest that female GAD patients – and older female patients in particular – may have decrements across a range of sexual functions that may need to be considered when discussing and choosing treatment options. In males, mean CSFQ total scores at baseline met the threshold for global SD in the older subgroup but not in the younger subgroup. However, CSFQ domain scores in both

age groups were lower than the SD thresholds. These results suggest that while overall concerns about sexual functioning may need to be discussed with older male GAD patients, all male patients with GAD may benefit from more targeted questions regarding specific sexual problems.

Given the prevalence of global SD found in this study population, along with the low baseline CSFQ domain scores found in both males and females, the potentially adverse effects of pharmacologic agents on sexual functioning need to be considered when treating patients with GAD. However, since sexual difficulties may also be linked to the core anxiousness experienced by GAD patients, choosing a medication that effectively reduces anxiety symptoms is also an important consideration. In patients who experienced a HAM-A response in the vilazodone GAD studies, mean improvements in CSFQ total score were found with both vilazodone and placebo, although there were no statistically significant differences between the treatment groups. At best, these changes suggest modest improvements in sexual functioning in treatment responders. More importantly, however, they indicate that male and female GAD patients who responded to vilazodone did not have concurrent worsening in sexual functioning. In other words, these results indicate that symptom improvements with vilazodone may outweigh potential negative serotonergic effects, such that patients may achieve anxiety relief without experiencing diminished sexual functioning.

Since underlying sexual difficulties associated with GAD could have been a confounding factor in evaluating the effects

of vilazodone on sexual functioning, subgroup analyses were conducted in males and females with or without baseline SD. In both treatment groups, greater mean improvements in CSFQ total score occurred in males and females with baseline SD than in patients without baseline SD, which may reflect a ceiling effect in the patients without baseline SD. By week 8, it seems some vilazodone-treated patients were experiencing therapeutic effects on SD, while others may have already experienced tolerance to these effects over time. For example, approximately 35% of male and female patients with SD at baseline switched to normal function status after 8 weeks of vilazodone treatment. In patients without SD at baseline, there was a significant mean worsening in CSFQ total score with vilazodone at week 4, but no significant difference from placebo was detected at week 8.

Although a greater percentage of patients with normal sexual functioning at baseline met SD criteria after treatment with vilazodone compared to placebo, >80% of patients in both treatment groups retained normal sexual functioning during the studies. One caveat to consider, however, is that these analyses were based on categorical shifts, but the categories themselves included a wide range of sexual symptom severity. For example, a male patient who had a CSFQ total score of 48 at baseline and a total score of 46 at the end of treatment would have been counted as a shift from normal functioning to SD; however, this <3 points change may not have been clinically meaningful.⁴⁰ The results thus need to be interpreted carefully. From this perspective, the shift analyses generally suggest that although some GAD patients without baseline SD may experience treatment-emergent SD with vilazodone, there is also a subset of patients with GAD-associated SD who may experience clinically meaningful improvements after acute treatment with vilazodone.

In these post hoc analyses, older males and females generally had worse CSFQ domain scores at baseline than younger patients. Small mean improvements in all CSFQ domain scores were found with vilazodone in older females, as well as in younger females and males. In older males, mean increases (improvements) were found in the domains of pleasure and arousal/erection; no change or very small mean decreases (−0.0 to −0.1) were found in the remaining domains of desire/frequency, desire/interest, and orgasm/ejaculation. However, it is important to emphasize that none of the vilazodone results in the sex-by-age analyses were statistically different from placebo, suggesting that this drug was not associated with worsening in any sexual functioning domain, regardless of sex or age.

AE reporting provides additional information on sexual issues that can arise during treatment, although the reported incidences may be lower than actual rates, since patients may be hesitant to discuss matters related to sexual function voluntarily.^{41,42} In this post hoc analysis, TEAEs related to sexual functioning were more common in patients treated with vilazodone than those treated with placebo, and more common in vilazodone-treated males than vilazodone-treated females. Decreased libido was the most common sexual function TEAE in vilazodone-treated female patients; four male placebo- and four male vilazodone-treated patients also reported decreased libido. The most common sexual function TEAEs for vilazodone-treated males were erectile dysfunction (2.4%) and delayed ejaculation (2.1%). By definition, the sexual function TEAEs reported here represent new or worsening conditions. Therefore, sexual problems that existed at baseline and subsequently resolved or improved are not included, making it difficult to compare TEAEs with changes in sexual function that were systematically assessed using a quantitative survey, such as the CSFQ.

Limitations of these analyses include their post hoc nature and lack of an active control; results should be interpreted accordingly. The exclusion of patients with concurrent psychiatric disorders limits the ability to generalize the results of this pooled study population to patients with comorbid MDD or significant depressive symptoms. Additionally, the constituent studies were not designed or powered to evaluate sexual function as a primary objective. For this reason, statistically significant between-group differences (or lack thereof) may not necessarily reflect clinical significance. Future studies that characterize SD in GAD in a broader patient population should be conducted to improve the clinical management of this disorder.

Conclusion

More than one-third of patients in the vilazodone GAD studies had SD at baseline, underscoring the importance of identifying sexual problems in patients with GAD. In clinical settings, patients may be uncomfortable talking about sexual difficulties, and the management of core anxiety symptoms may be a more pressing issue for the health care provider. However, sexual health is an important component of a patient's overall well-being, and treatment-related SD can reduce medication adherence.⁴ Therefore, inquiring about specific changes in sexual functioning should be incorporated into the overall treatment strategy. Because SD can encompass a range of issues, from lack of desire/interest to inability to perform, specific questions may need to be

asked to pinpoint the types of problems a patient might be experiencing. One way to broach this potentially sensitive subject may be to explain the possible adverse effects that various medications may have on sexual functioning. Regardless of the method of inquiry, SD in GAD remains an underrecognized clinical problem that warrants ongoing attention and discussion.

In the GAD studies that were included in the current post hoc analyses, changes in CSFQ total and domain scores after 8 weeks of double-blind treatment showed no significant differences between vilazodone 20–40 mg/day and placebo. One advantage of using the CSFQ in clinical trials is that the instrument is sex-specific, with established criteria for SD in both males and females. The CSFQ analyses presented in this report indicate that vilazodone was not associated with increased sexual deficits in either males or females, regardless of age. Moreover, among treatment responders (defined as patients with $\geq 50\%$ improvement in anxiety symptoms based on HAM-A total score change from baseline), vilazodone was associated with modest improvements in SD; these effects were particularly noticeable among females who responded to treatment. Patients with global SD at baseline also experienced improvements in sexual functioning, with approximately 35% of males and females with baseline SD shifting to normal sexual functioning after 8 weeks of vilazodone treatment. TEAEs related to sexual functioning were observed with vilazodone in some patients, more frequently in males than in females. Although these potential negative effects need to be considered, the results of this post hoc analysis suggest that the negative impact of vilazodone on sexual functioning is generally limited in adults with GAD, which is consistent with the effects seen in patients with MDD.^{8,40} Such information, along with findings from other antidepressant trials,^{6,43} may help clinicians select medications with efficacy and safety profiles that are appropriate for each individual patient.

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