# Effects of vilazodone on sexual functioning in healthy adults: results from a randomized, double-blind, placebo-controlled, and active-controlled study

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**The aim of this study is to evaluate the effects of vilazodone on sexual functioning in healthy, sexually active adults and assess the impact of medication nonadherence in this type of trial. Participants were randomized to vilazodone (20 or 40 mg/day), paroxetine (20 mg/day), or placebo for 5 weeks of double-blind treatment. The primary endpoint was change from baseline to day 35 in Change in Sexual Functioning Questionnaire (CSFQ) total score in the intent-to-treat (ITT) population. Post-hoc analyses were carried out in modified intent-to-treat (mITT) populations that excluded participants in the active-treatment groups with undetectable plasma drug concentrations at all visits (mITT-I) or at least one visit (mITT-II). In the ITT population ($N = 199$), there were no statistically significant differences between any treatment groups for CSFQ total score change: placebo, −1.0; vilazodone 20 mg/day, −1.4; vilazodone 40 mg/day, −1.9; and paroxetine, −3.5. In mITT-I ($N = 197$) and mITT-II ($N = 159$), CSFQ total score change was not significantly different between vilazodone (either dose) versus placebo; the CSFQ total score decreased significantly ($P < 0.05$) with paroxetine versus both placebo and vilazodone 20 mg/day, but not versus vilazodone 40 mg/day. Vilazodone exerted no significant effect on sexual functioning in healthy adults. Medication nonadherence can alter study results and may be an important consideration in trials with volunteer participants.** *Int Clin Psychopharmacol* **32:27–35** 

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## Introduction

Sexual dysfunction, which is characterized by a clinically significant impairment in sexual desire, sexual response, or ability to experience sexual pleasure (APA, 2013), is commonly observed in patients with major depressive disorder (MDD). The relationship between sexual dysfunction and depression is bidirectional, with sexual symptoms generally arising from neurobiologic changes that are related to the disorder itself (Clayton *et al.*, 2014).

The relationship between sexual dysfunction and depression is further complicated by potentially adverse effects of medications such as selective serotonin reuptake inhibitors (SSRIs), which have been associated with sexual dysfunction in 40–70% of treated patients (Kennedy and Rizvi, 2009). The mechanisms by which SSRIs negatively affect sexual functioning are not completely known, but serotonin is considered an important inhibitory neurotransmitter in the regulation of sexual behavior as well as a key element in the pathogenesis of mood and anxiety disorders (Olivier, 2015). Medications such as buspirone, a 5-$HT_{1A}$ receptor partial agonist, have been used to mitigate SSRI treatment-emergent sexual dysfunction. Preclinical studies in male rats have shown 5-$HT_{1A}$ receptor agonists to activate postsynaptic receptors in limbic areas of the brain that facilitate ejaculatory behaviors (Bijlsma *et al.*, 2014). In one study, decreased sexual behaviors in male rats were observed following chronic treatment with SSRIs (citalopram, paroxetine), but not vilazodone, an SSRI and 5-$HT_{1A}$ partial agonist (Oosting *et al.*, 2016).

Vilazodone has been approved for the treatment of MDD in adults (Forest Laboratories, 2013) and evaluated in generalized anxiety disorder (Durgam *et al.*, 2016; Gommoll *et al.*, 2015a, 2015b). The effects of vilazodone on sexual functioning were found to be small and similar to placebo in patients with MDD (Clayton *et al.*, 2013) or generalized anxiety disorder (Durgam *et al.*, 2016; Gommoll *et al.*, 2015a, 2015b), as assessed using the Changes in Sexual Functioning Questionnaire (CSFQ) (Clayton *et al.*, 1997a). Consistent with the US Food and Drug Administration

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(FDA) recommendations for the evaluation of sexual dysfunction in antidepressant clinical trials (Khin *et al*., 2015), a randomized, placebo-controlled study in healthy volunteers was carried out recently to evaluate the effects of vilazodone on sexual functioning in the absence of a major psychiatric disorder. Post-hoc analyses that excluded participants who were randomized to active treatment, but had undetectable plasma drug concentrations, were also carried out to explore whether medication nonadherence influenced the results.

## Participants and methods

### Study design and treatment

This was a randomized, double-blind, parallel-group, phase I study (NCT02097147) that compared the effects of placebo, paroxetine (20 mg/day), and vilazodone (20 or 40 mg/day) on sexual function in healthy, sexually active adults. As paroxetine at standard clinical doses has been associated with sexual dysfunction (Clayton *et al*., 2002), it was selected as an active comparator and to test for overall sensitivity of the trial (i.e. assay sensitivity). The study was carried out at four centers in the USA from March to November 2014 in full compliance with the FDA guidelines for good clinical practice and in accordance with the Declaration of Helsinki. Each center's institutional review board approved the study. All volunteer participants provided written informed consent.

The study included a 2-week screening period, 5 weeks of double-blind treatment, and a 1-week down-taper period. Participants were randomized (1 : 1 : 1 : 1) to the following once-daily treatments: placebo (35 days); paroxetine 20 mg/day [10 mg/day (7 days), 20 mg/day (28 days)]; vilazodone 20 mg/day [10 mg/day (7 days), 20 mg/day (28 days)]; and vilazodone 40 mg/day [10 mg/day (7 days), 20 mg/day (7 days), 40 mg/day (21 days)]. Allocation of treatment was implemented using computer-generated participant identification numbers and drug assignment randomization codes. All participants, investigators, and study site personnel were blinded to treatment allocation. Study drugs (paroxetine, vilazodone, and matching placebo capsules) were identical in size, shape, color, and packaging. Breaking of the blind for any reason resulted in discontinuation from the study.

For study-center dosing, administered at 8:00 a.m. at all visits during double-blind treatment (days 1, 8, 15, 22, and 35), participants received medication under the direct supervision of study-center personnel. For at-home dosing, adherence was monitored by pill count (number dispensed and returned) and by participants' daily records (number of pills taken and time taken). Poor adherence, defined as less than 80% or more than 120% of the required medication on the basis of pill count, resulted in discontinuation from the study upon approval of the study sponsor.

For pharmacokinetic analyses and further assessment of medication adherence, blood samples were obtained within 15 min before study-center dosing at each postbaseline study visit (days 8, 15, 22, and 35). Methods for evaluating plasma drug concentrations are summarized in Appendix 1 (Supplemental digital content 1, *http://links.lww.com/ICP/A21*).

### Eligibility criteria

The study included healthy men and women, ages 18–45 years, who had engaged in sexual activity at least twice a week for the past 3 months and were willing to continue sexual activity throughout the study. All participants were required to use effective contraception (men and women), be nonsmokers, and have a BMI of at least 18 and up to 35 kg/m$^2$ with a sitting pulse rate of at least 50 and of up to 110 bpm.

Individuals with sexual dysfunction at screening (CSFQ total score $\leq$47 for men or $\leq$41 for women) were excluded from the study. Other key exclusion criteria were pregnancy, history of sexual disorder (e.g. erectile dysfunction, premature ejaculation), diagnosis of any psychiatric disorder (current or within the past 3 years), clinically significant medical history or current medical condition (per investigator judgment), abnormal exams (physical, vital signs, laboratory tests) at screening, substance abuse or dependence (current or within the past 5 years), and suicide risk on the basis of the Columbia-Suicide Severity Rating Scale (C-SSRS) or investigator judgment.

No medications were allowed for at least 14 days before day 1 of the study and throughout the rest of the study, except for hormonal contraceptives and the following drugs as needed: aspirin and nonsteroidal anti-inflammatory drugs, antidiarrheal preparations and antiemetics, antihistamines, H2-blockers and proton pump inhibitors, laxatives, and sedatives/hypnotics (for sleep).

### Patient populations

The safety population included all randomized patients who received at least one dose of the study drug. The intent-to-treat (ITT) population included all participants in the safety population who had at least one available postbaseline CSFQ assessment. On the basis of predose plasma drug concentrations, two modified ITT (mITT) populations were defined post-hoc as follows: mITT-I, which excluded any participant in active-treatment groups who had no detectable plasma drug concentration at all postbaseline study visits; and mITT-II, which excluded any participant in active-treatment groups who had no detectable plasma drug concentration at any postbaseline study visit.

### Outcome measure

The CSFQ, a 14-item self-report instrument that has been validated in psychiatric patients and healthy individuals, is a standard tool in antidepressant trials. The total score (range: 14–70) is calculated by summing

individual item scores (range: 1–5 each). The CSFQ encompasses five subscales that evaluate the following areas of sexual function: pleasure, desire/frequency, desire/interest, arousal/erection or arousal/excitement, and orgasm/ejaculation or orgasm/completion (Clayton *et al.*, 1997a, 1997b). Each subscale includes one to three items; no item is included in more than one domain. Item 14 (frequency of painful orgasm) and item 10 (sex-specific arousal difficulties) are not included in any subscale.

### Primary outcome analysis

The predefined primary outcome parameter was change from baseline to day 35 in the CSFQ total score in the ITT population. Superiority tests comparing each vilazodone dose (20 and 40 mg/day) with paroxetine 20 mg/day were performed on the basis of the number of participants with an available CSFQ total score assessment (i.e. observed cases) using a mixed model for repeated measures (MMRM) with treatment group, sex, study center, study day, and treatment group-by-study day as fixed effects and baseline value and baseline-by-study day as covariates. An unstructured covariance matrix was used to model covariance of within-participant scores. The Kenward–Roger approximation was used to estimate denominator degrees of freedom. Comparison testing between each active treatment and placebo was also performed using the MMRM method described above, with the paroxetine–placebo comparison used to assess assay sensitivity.

### Post-hoc analyses

Change from baseline to day 35 in CSFQ total score was analyzed in the mITT-I and mITT-II populations, as well as by sex (men and women) in each of the three study populations (ITT, mITT-I, and mITT-II). Analyses were only carried out in participants with an available CSFQ assessment; for participants in the mITT-I or mITT-II population who were randomized to active treatment, detectable plasma drug concentrations (vilazodone or paroxetine) at day 35 were also required for analysis. The MMRM method described above was applied, but without sex as a fixed effect in the separate analyses of men and women. Using established CSFQ total score criteria ($\leq 47$ for men and $\leq 41$ for women), the percentages of men and women in the mITT-I and mITT-II populations with sexual dysfunction at each postbaseline study visit (days 8, 15, 22, and 35) were analyzed descriptively. In addition, changes from baseline to day 35 in CSFQ subscale scores (MMRM) were analyzed by sex in the mITT-I and mITT-II populations. Again, these analyses were based on participants with available CSFQ assessments and, in the active-treatment groups, detectable plasma drug concentrations at the study visit analyzed (observed cases).

### Safety analyses

Safety outcomes were analyzed descriptively. Adverse events (AEs) were defined as untoward medical occurrences that were reported from the time of informed consent until 30 days after the last dose of study drug. Physical exams, laboratory tests, and ECG were performed at screening and at the end of the study; vital signs and the C-SSRS were performed at screening and all study visits.

## Results

### Participants

Of the 202 participants included in the safety population, 170 (84.2%) completed the study; AEs were the most common reason for premature discontinuation in all active-treatment groups (Table 1). Three participants (one paroxetine, two vilazodone, 40 mg/day) did not have available postbaseline CSFQ assessments and were excluded from the ITT population ($N = 199$).

On the basis of predose plasma drug concentrations (Appendix I: Supplemental digital content 1, *http://links.lww.com/ICP/A21*), two participants in the ITT population (one each from the vilazodone 20 and 40 mg/day groups) had no detectable active drug in plasma at all study visits (mITT-I, $N = 197$); 40 participants had no detectable active drug in plasma at one or more study visits (mITT-II, $N = 159$).

Demographics in the safety population were similar across all treatment groups (Table 1). The mean baseline CSFQ total scores were similar across treatment groups in the ITT population and both mITT populations.

### Change in Sexual Functioning Questionnaire total score changes

#### *Primary outcome analysis*

In the ITT population, a mean decrease (worsening) from baseline to day 35 in the CSFQ total score was found in all treatment groups (Fig. 1a). No statistically significant differences were detected for any of the planned comparisons between treatment groups. The lack of significance for paroxetine versus placebo indicated that the trial was unable to demonstrate a significant effect for the active control (i.e. the trial lacked assay sensitivity).

#### *Post-hoc analyses*

At day 35 in the mITT-I and mITT-II populations (excluding participants in the active-treatment groups who had no detectable plasma drug concentrations at this study visit), there was no statistical difference between vilazodone (either dose) and placebo for the mean change in the CSFQ total score (Fig. 1a). However, paroxetine-treated participants had significantly greater mean worsening in the CSFQ total score than participants who received placebo. In addition, vilazodone 20 mg/day showed significantly less mean worsening in the CSFQ

**Table 1 Study participants**

| | Placebo | Paroxetine (20 mg/day) | Vilazodone (20 mg/day) | Vilazodone (40 mg/day) |
|---|---|---|---|---|
| Study populations | | | | |
| Randomized population (*n*) | 51 | 49 | 50 | 52 |
| Safety population (*n*) | 51 | 49 | 50 | 52 |
| ITT population (*n*) | 51 | 48 | 50 | 50 |
| mITT-I population (*n*)[a] | 51 | 48 | 49 | 49 |
| mITT-II population (*n*)[b] | 51 | 29 | 41 | 38 |
| Participant disposition (safety population) | | | | |
| Discontinued from study (*n*) | 6 | 6 | 7 | 13 |
| Adverse event | 1 | 3 | 4 | 5 |
| Protocol violation | 2 | 1 | 1 | 1 |
| Withdrawal of consent | 1 | 1 | 1 | 4 |
| Lost to follow-up | 1 | 1 | 1 | 3 |
| Other | 1 | 0 | 0 | 0 |
| Completed study (*n*) | 45 | 43 | 43 | 39 |
| Baseline demographics (safety population) | | | | |
| Age [mean (SD)] (years) | 29.9 (7.7) | 31.3 (7.7) | 30.6 (7.0) | 29.7 (6.6) |
| Women [*n* (%)] | 31 (60.8) | 30 (61.2) | 32 (64.0) | 33 (63.5) |
| Race [*n* (%)] | | | | |
| White | 29 (56.9) | 34 (69.4) | 31 (62.0) | 29 (55.8) |
| Black/African-American | 19 (37.3) | 13 (26.5) | 16 (32.0) | 22 (42.3) |
| BMI [mean (SD)] (kg/m$^2$) | 26.2 (3.9) | 25.8 (4.8) | 27.3 (4.1) | 27.6 (4.6) |
| CSFQ total score (ITT and mITT populations) | | | | |
| Mean baseline score (SD) | | | | |
| ITT population | 58.5 (6.7) | 59.0 (4.8) | 59.8 (6.4) | 59.3 (6.4) |
| mITT-I population[a] | 58.5 (6.7) | 59.0 (4.8) | 59.6 (6.3) | 59.2 (6.5) |
| mITT-II population[b] | 58.5 (6.7) | 60.0 (4.1) | 58.8 (6.3) | 59.7 (6.7) |

CSFQ, Changes in Sexual Functioning Questionnaire; ITT, intent-to-treat; mITT, modified intent-to-treat.
[a]Excludes participants in active-treatment groups with no detectable plasma drug concentration at all postbaseline visits.
[b]Excludes participants in active-treatment groups with no detectable plasma drug concentration at any postbaseline visit.

total score than paroxetine in both the mITT-I and the mITT-II populations.

Among men, the mean decrease in the CSFQ total score was significantly greater with paroxetine versus placebo in the mITT-I and mITT-II populations, but not in the ITT population (Fig. 1b). Men in the mITT-II population also had significantly less mean worsening in the CSFQ total score with vilazodone 20 mg/day versus paroxetine. No significant differences between vilazodone (20 or 40 mg/day) and placebo were detected among men in any study population. Among women, no statistical differences between active treatment and placebo, or between vilazodone and paroxetine, were detected in any of the three study populations (Fig. 1c).

### Change in Sexual Functioning Questionnaire sexual dysfunction by study visit

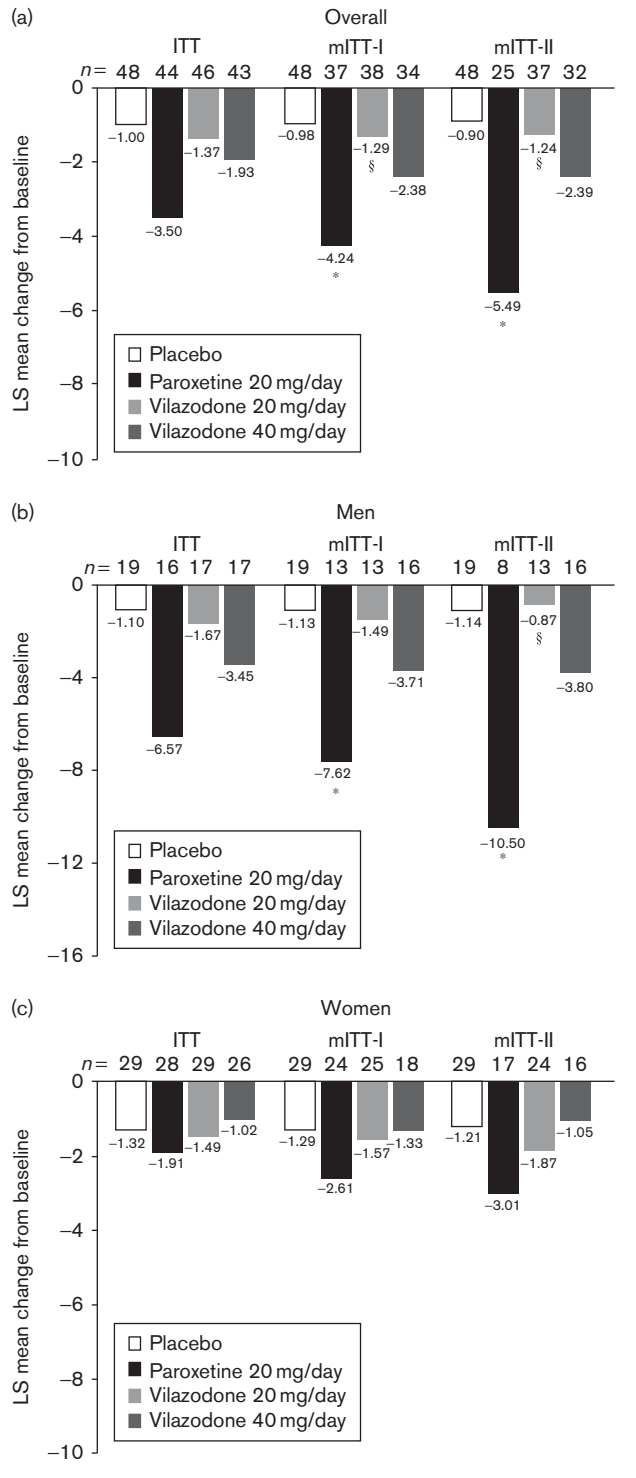
In the mITT-I population, sexual dysfunction in men with detectable plasma levels of active drug was first observed at day 15 (paroxetine, 23.1%; vilazodone 40 mg/day, 12.5%) (Fig. 2a). The percentage of men reporting sexual dysfunction was not statistically significant between any treatment group at any time point. However, men in the paroxetine group had the highest incidence of sexual dysfunction relative to all other treatment groups at days 15, 22, and 35. Sexual dysfunction in women was not observed with vilazodone 20 or 40 mg/day at any visit (Fig. 2b). Results in the mITT-II population were similar to those in the mITT-I population, as shown in Supplementary Fig. 1 (Supplemental digital content 1, *http://links.lww.com/ICP/A21*).

### Change in Sexual Functioning Questionnaire subscale score changes

In the mITT-I and mITT-II populations (with detectable plasma levels of active drug), the mean decreases in CSFQ subscale scores were greater in men than in women at day 35, as shown in Fig. 3 and Supplementary Fig. 2 (Supplemental digital content 1, *http://links.lww.com/ICP/A21*). Men who received vilazodone 20 mg/day showed a small mean improvement in desire/interest that was statistically significant compared with paroxetine. No significant difference between vilazodone (20 or 40 mg/day) and placebo was found in any CSFQ subscale, either in men or in women.

Among women, no significant differences between paroxetine and placebo were found in any CSFQ subscale (Fig. 3b, Supplementary Fig. 2B, Supplemental digital content 1, *http://links.lww.com/ICP/A21*). However, men in the mITT-I population had significantly greater worsening with paroxetine versus placebo in arousal/erection and orgasm/ejaculation (Fig. 3a), whereas men in the mITT-II population had significantly greater worsening with paroxetine versus placebo in all CSFQ subscales except desire/interest (Supplementary Fig. 2A, Supplemental digital content 1, *http://links.lww.com/ICP/A21*). Men in the mITT-II population also had significantly less worsening with vilazodone versus paroxetine in pleasure (20 mg/day), orgasm/ejaculation (20 mg/day),

**Fig. 1**




Change from baseline to day 35 in the CSFQ total score (MMRM). Sample size (*n*-value) represents the number of participants in each treatment group who had an available CSFQ total score assessment at day 35. For the mITT-I and mITT-II analyses, participants in the vilazodone and paroxetine groups with undetectable plasma drug concentrations at day 35 were excluded. *$P < 0.05$, active drug versus placebo; §$P < 0.05$, vilazodone versus paroxetine. CSFQ, Changes in Sexual Functioning Questionnaire; ITT, intent-to-treat; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

and arousal/erection (both doses), as well as a small mean improvement in desire/interest (20 mg/day) that was significantly different from paroxetine.

### Safety and tolerability

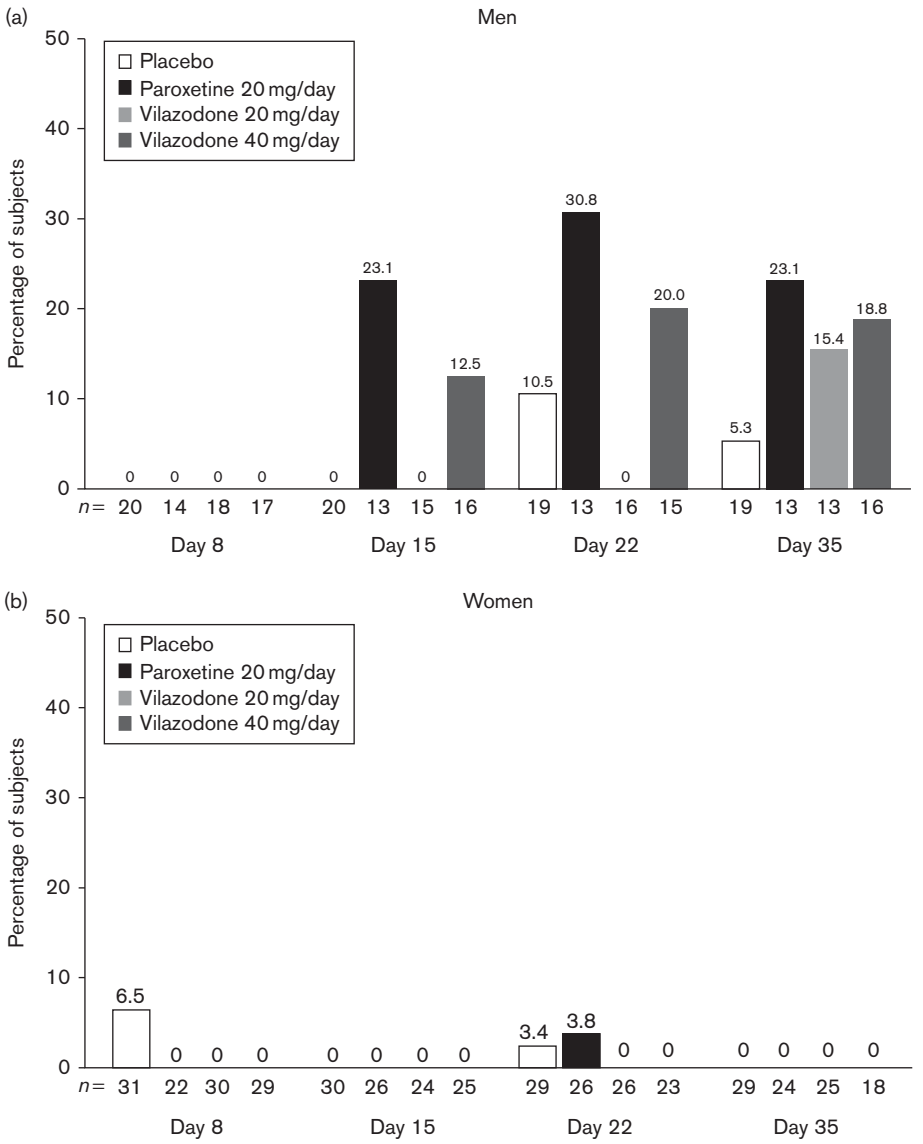
Treatment-emergent AEs (TEAEs) were more frequently observed with active treatment than with placebo (Table 2). Discontinuations because of AEs were similar across active-treatment groups. One serious AE (appendicitis) was reported and judged by the investigator as unrelated to treatment; no deaths occurred in the study. No TEAE related to sexual dysfunction was found in more than one participant in any treatment group. No clinically relevant findings were found for vital signs, ECGs, or clinical laboratory tests. C-SSRS monitoring indicated no suicidal behaviors during double-blind treatment. One paroxetine-treated participant (a 32-year-old man) who had active suicidal ideation (with specific plan and intent) was excluded from the study.

## Discussion

On the basis of the predefined primary outcome parameter (i.e. CSFQ total score change from baseline to day 35 in the ITT population, observed cases analysis), both doses of vilazodone (20 and 40 mg/day) had less impact on sexual functioning in sexually active, healthy adults compared with paroxetine 20 mg/day, but the differences were not statistically significant. Compared with placebo, paroxetine showed a larger but statistically nonsignificant decrease in the CSFQ total score, indicating that the trial lacked assay sensitivity. This nonsignificant result for the active control (paroxetine vs. placebo) led to further analyses for possible explanations, including nonadherence to treatment using plasma drug concentrations as a proxy.

Healthy volunteers who participate in clinical studies do not expect to receive any health benefits from treatment, and without this type of 'incentive,' may not adhere to treatment. In the current study, it appears that a number of participants who were randomized to active treatment did not take study drug dose(s) at home as directed, on the basis of undetectable predose plasma concentrations. To investigate the effect of nonadherence on the primary analysis outcome, post-hoc analyses were carried out in two modified ITT populations that excluded participants in the active-treatment groups with undetectable plasma drug concentrations at all study visits (mITT-I) or at any study visit (mITT-II). In both of these populations, worsening in the CSFQ total score was significantly greater with paroxetine compared with placebo. In addition, the CSFQ total score worsening was significantly less with vilazodone 20 mg/day compared with paroxetine. These differences were more pronounced in men. In women, no significant differences between active treatment and placebo or between paroxetine and vilazodone were detected in the ITT population or either mITT population.

**Fig. 2**

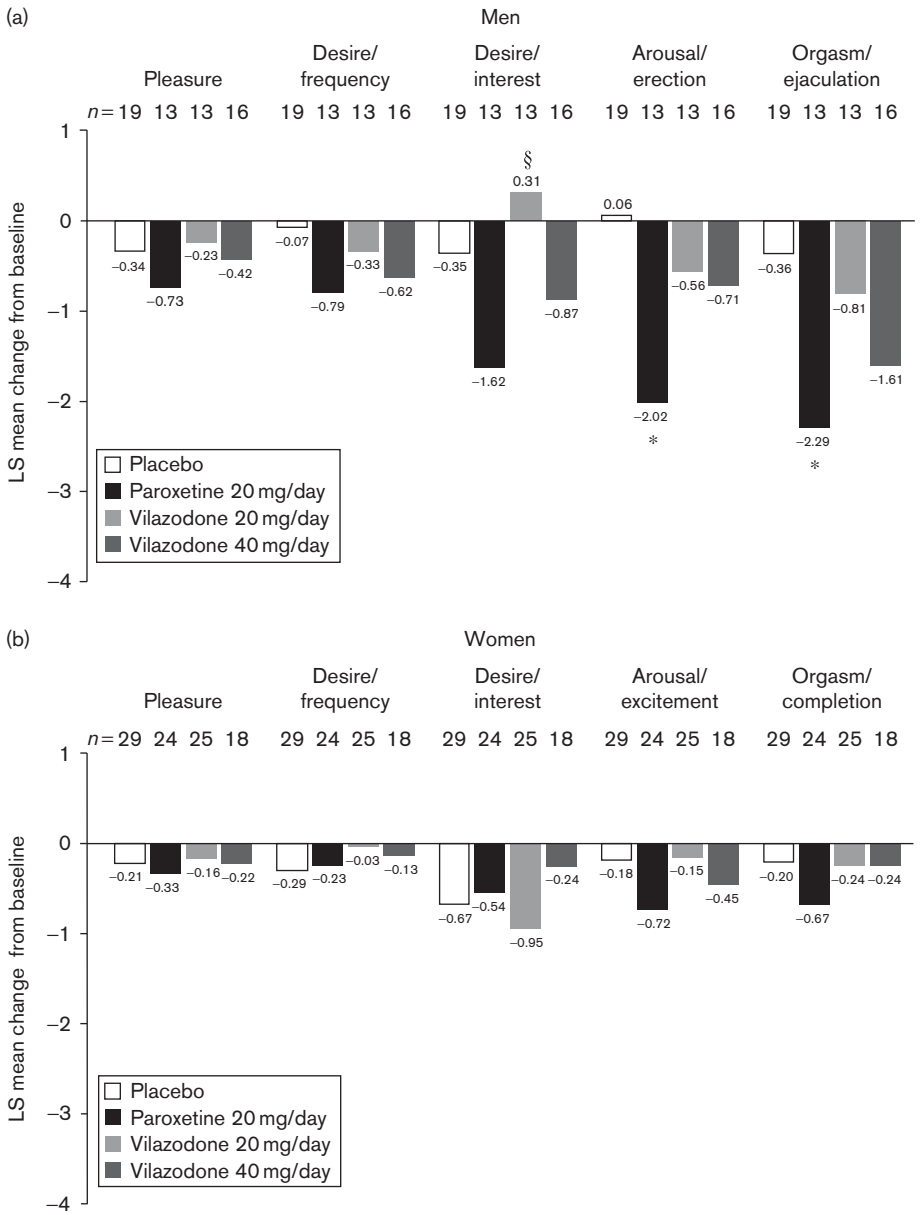



CSFQ sexual dysfunction by study visit (mITT-I population). Sexual dysfunction defined as CSFQ total score ≤47 (men) or ≤41 (women). Sample size (*n*-value) represents the number of participants in each treatment group who had an available CSFQ total score assessment at the study visit analyzed (day 8, 15, 22, or 35) and, in the active-treatment groups, had detectable plasma drug concentrations at the respective visit. CSFQ, Changes in Sexual Functioning Questionnaire; mITT, modified intent-to-treat.

As with other SSRIs (Rosen *et al.*, 1999), the effects of vilazodone on sexual functioning appear to have been dose related. In addition to the smaller mean CSFQ total score changes found with vilazodone 20 mg/day relative to vilazodone 40 mg/day and paroxetine, sexual dysfunction in men receiving vilazodone 20 mg/day was not observed until day 35 in both mITT populations. Within recommended prescribing guidelines, vilazodone dosing in patients may therefore need to be adjusted to balance the clinical benefits of this medication against any adverse effects, including sexual dysfunction.

In the male mITT-I population, the mean decreases in the CSFQ domains of arousal/erection and orgasm/ejaculation were significantly greater with paroxetine than placebo, which is consistent with the sexual side-effect profile of SSRIs in men (Rosen *et al.*, 1999). In the male mITT-II population, significant differences between paroxetine and placebo were also found in pleasure and desire/frequency, but the magnitude of worsening was smaller than that in the CSFQ subscales related to the arousal and orgasm phases of the sexual response cycle. Men in the mITT-I and mITT-II populations showed a small mean improvement with vilazodone 20 mg/day in

**Fig. 3**




Change from baseline to day 35 in CSFQ subscale scores (mITT-I population, MMRM). Sample size (*n*-value) represents the number of participants in each treatment group who had available CSFQ subscale score assessments at day 35, and, in the active-treatment groups, had detectable plasma drug concentrations at day 35.*$P < 0.05$, active drug versus placebo; §$P < 0.05$, vilazodone versus paroxetine. CSFQ, Changes in Sexual Functioning Questionnaire; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

the desire/interest domain that was significantly different from the worsening found with paroxetine. It is somewhat difficult to interpret this result as decreased desire in men may have been related to delayed or absent ejaculation (Rosen *et al.*, 1999).

The mITT population results, which excluded participants in the active-treatment groups with undetectable plasma drug concentrations at specified study visits, highlight several important points on nonadherence. Specifically, exclusion of participants in the active-treatment groups who had undetectable plasma drug concentrations at day 35 resulted in statistically significant differences in the CSFQ total score change for paroxetine versus placebo and paroxetine versus vilazodone 20 mg. These statistically significant findings in the modified ITT populations suggest that data from 'professional participants' (Czobor and Skolnick, 2011) or nonadherent participants can skew results, but addressing this problem is a complicated matter. As was done in

**Table 2 Adverse events (safety population)**

| | *n* (%) | | | |
|---|---|---|---|---|
| | Placebo (*n* = 51) | Paroxetine (20 mg/day) (*n* = 49) | Vilazodone (20 mg/day) (*n* = 50) | Vilazodone (40 mg/day) (*n* = 52) |
| AE summary | | | | |
| Any TEAE | 21 (41.2) | 29 (59.2) | 41 (82.0) | 33 (63.5) |
| Discontinuation because of AE | 1 (2.0) | 3 (6.1) | 4 (8.0) | 5 (9.6) |
| Any serious AE | 0 | 0 | 1 (2.0) | 0 |
| Common TEAEs[a] | | | | |
| Headache | 9 (17.6) | 7 (14.3) | 11 (22.0) | 13 (25.0) |
| Nausea | 2 (3.9) | 7 (14.3) | 19 (38.0) | 12 (23.1) |
| Vomiting | 2 (3.9) | 2 (4.1) | 9 (18.0) | 8 (15.4) |
| Diarrhea | 2 (3.9) | 4 (8.2) | 11 (22.0) | 6 (11.5) |
| Somnolence | 3 (5.9) | 6 (12.2) | 5 (10.0) | 6 (11.5) |
| Dizziness | 3 (5.9) | 5 (10.2) | 6 (12.0) | 4 (7.7) |
| Insomnia | 1 (2.0) | 1 (2.0) | 4 (8.0) | 3 (5.8) |
| Upper respiratory tract infection | 1 (2.0) | 1 (2.0) | 0 | 3 (5.8) |
| Abdominal discomfort | 1 (2.0) | 2 (4.1) | 5 (10.0) | 2 (3.8) |
| Fatigue | 0 | 4 (8.2) | 0 | 1 (1.9) |
| TEAEs related to sexual functioning[b] | | | | |
| Sexual dysfunction | 0 | 1 (2.0) | 1 (2.0) | 1 (1.9) |
| Ejaculation delayed[c] | 0 | 0 | 1 (5.6) | 0 |
| Spontaneous penile erection[c] | 0 | 0 | 1 (5.6) | 0 |
| Vulvovaginal pain[c] | 0 | 0 | 1 (3.1) | 0 |
| Ejaculation disorder[c] | 0 | 1 (5.3) | 0 | 0 |
| Libido decreased | 0 | 1 (2.0) | 0 | 0 |

AE, adverse event; TEAE, treatment-emergent adverse event.
[a]Reported in ≥ 5% of participants in any active-treatment group.
[b]Reported in ≥ 2% of participants in any active-treatment group.
[c]Percentage relative to the number of participants of the appropriate sex.

this study, collection of blood samples to evaluate plasma drug concentrations may be an optimal strategy for monitoring adherence, but potential study participants may consider regular blood draws to be an unreasonable burden (Osterberg and Blaschke, 2005). Moreover, blood sample monitoring does not prevent participants from skipping doses between visits and only taking medication before a visit. Other strategies that might improve adherence include newer technologies such as electronic recording of bottle opening, ingestible sensors to track medication adherence (e.g. Proteus sensor, Proteus Digital Health, Inc., Redwood City, California, USA), and automated reminder messages to participants (Dicarlo, 2012; Dekoekkoek *et al.*, 2015; Alili *et al.*, 2016).

Participants excluded from the mITT-II population took the assigned medication, but stopped at least once during the study, possibly because of undesirable side effects. The percentage of excluded participants relative to the predefined ITT population was higher with paroxetine [39.6% (19/48)] than with vilazodone 20 mg/day [18.0% (9/50)] or vilazodone 40 mg/day [24.0% (12/50)], which may need to be considered when interpreting the AE results. If the 40 participants who were excluded from the mITT-II population temporarily discontinued treatment to alleviate adverse side effects, TEAEs in active-treatment groups need to be interpreted with some caution. For example, although the overall incidence of TEAEs was lower with paroxetine than either dose of vilazodone, the data may be confounded by the higher percentage of paroxetine-treated participants who had no detectable plasma drug concentrations at one or more study visits. Conversely, the relatively high incidence of TEAEs in the vilazodone 20 mg/day group may reflect the fact that this group had the lowest number of non-adherent participants. It seems reasonable to expect that TEAEs would be reported more frequently in participants who adhered to treatment than in participants who interrupted treatment for any reason.

Sexual dysfunction has been associated with non-treatment-related factors such as age, sex, race, medical comorbidities, employment status, and childhood trauma (Beutel *et al.*, 2008; Appa *et al.*, 2014; Salonia *et al.*, 2014; Hughes *et al.*, 2015). Although sex was included in the current analyses, the study was too small (~50 participants per treatment group) and the age range was too narrow (18–45 years) to carry out meaningful subset analyses using other potential risk factors for sexual dysfunction. However, factors such as age and race may need to be considered when selecting antidepressants for individuals requiring psychiatric treatment.

A limitation of this study was the short treatment period. Although the results provide information on the acute effects of vilazodone in healthy individuals with no current or previous history of sexual dysfunction, the generalizability of these results to long-term effects in individuals who do not have sexual dysfunction but require antidepressant treatment for a psychiatric illness is uncertain.

## Conclusion

This double-blind, placebo-controlled and active-controlled, multiple-dose study was carried out to compare the effects on sexual functioning in healthy volunteers treated with vilazodone (20 or 40 mg/day) or paroxetine (20 mg/day), with comparison between paroxetine and placebo included for assay sensitivity. For the predefined primary outcome parameter, there were numeric but not statistically significant differences between vilazodone (both doses) and paroxetine. As the difference between paroxetine and placebo was also nonsignificant, assay sensitivity was not found. However, in analyses that excluded participants in the active-treatment groups with nondetectable plasma drug levels, statistically significant differences between paroxetine and placebo (and between vilazodone 20 mg/day and paroxetine) were detected for the CSFQ total score change from baseline to day 35. Worsening of sexual functioning was generally greater in men than in women, with the most pronounced effects found in male participants randomized to paroxetine. No significant differences between vilazodone 20 or 40 mg/day and placebo were detected in any outcome measure. The evidence of

nonadherence in this study indicates how results can be altered when some participants do not take study medication as directed. It also underscores the need for monitoring compliance in clinical trials and even possibly including compliance as part of the primary outcome, particularly in studies of healthy volunteers (as recommended by FDA for studies of antidepressants and sexual dysfunction) who do not expect to benefit from treatment.

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### Conflicts of interest

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## References

APA (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Arlington, VA: American Psychiatric Association.

Appa AA, Creasman J, Brown JS, Van Den Eeden SK, Thom DH, Subak LL, Huang AJ (2014). The impact of multimorbidity on sexual function in middle-aged and older women: beyond the single disease perspective. *J Sex Med* **11**:2744–2755.

Beutel ME, Stöbel-Richter Y, Brähler E (2008). Sexual desire and sexual activity of men and women across their lifespans: results from a representative German community survey. *BJU Int* **101**:76–82.

Bijlsma EY, Chan JS, Olivier B, Veening JG, Millan MJ, Waldinger MD, Oosting RS (2014). Sexual side effects of serotonergic antidepressants: mediated by inhibition of serotonin on central dopamine release? *Pharmacol Biochem Behav* **121**:88–101.

Clayton AH, McGarvey EL, Clavet GJ (1997a). The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. *Psychopharmacol Bull* **33**:731–745.

Clayton AH, McGarvey EL, Clavet GJ, Piazza L (1997b). Comparison of sexual functioning in clinical and nonclinical populations using the Changes in Sexual Functioning Questionnaire (CSFQ). *Psychopharmacol Bull* **33**:747–753.

Clayton AH, Pradko JF, Croft HA, Montano CB, Leadbetter RA, Bolden-Watson C, *et al.* (2002). Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* **63**:357–366.

Clayton AH, Kennedy SH, Edwards JB, Gallipoli S, Reed CR (2013). The effect of vilazodone on sexual function during the treatment of major depressive disorder. *J Sex Med* **10**:2465–2476.

Clayton AH, El Haddad S, Iluonakhamhe J-P, Ponce Martinez C, Schuck AE (2014). Sexual dysfunction associated with major depressive disorder and antidepressant treatment. *Expert Opin Drug Saf* **13**:1361–1374.

Czobor P, Skolnick P (2011). The secrets of a successful clinical trial: compliance, compliance, and compliance. *Mol Interv* **11**:107–110.

DeKoekkoek T, Given B, Given CW, Ridenour K, Schueller M, Spoelstra SL (2015). mHealth SMS text messaging interventions and to promote medication adherence: an integrative review. *J Clin Nurs* **24** (19–20):2722–2735.

DiCarlo LA (2012). Role for direct electronic verification of pharmaceutical ingestion in pharmaceutical development. *Contemp Clin Trials* **33**:593–600.

Durgam S, Gommoll C, Forero G, Nunez R, Tang X, *et al.* (2016). Efficacy and safety of vilazodone in patients with generalized anxiety disorder: a randomized, double-blind, placebo-controlled, flexible-dose trial. *J Clin Psychiatry* [Epub ahead of print].

El Alili M, Vrijens B, Demonceau J, Evers SM, Hiligsmann M (2016). A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. *Br J Clin Pharmacol* **82**:268–279.

Forest Laboratories (2013). *Fetzima [prescribing information]*. New York, NY: Forest Laboratories Inc.

Gommoll C, Durgam S, Mathews M, Forero G, Nunez R, Tang X, Thase ME (2015a). A double-blind, randomized, placebo-controlled, fixed-dose phase III study of vilazodone in patients with generalized anxiety disorder. *Depress Anxiety* **32**:451–459.

Gommoll C, Forero G, Mathews M, Nunez R, Tang X, *et al.* (2015b). Vilazodone in patients with generalized anxiety disorder: a double-blind, randomized, placebo-controlled, flexible-dose study. *Int Clin Psychopharmacol* **30**: 297–306.

Hughes AK, Rostant OS, Pelon S (2015). Sexual problems among older women by age and race. *J Womens Health (Larchmt)* **24**:663–669.

Kennedy SH, Rizvi S (2009). Sexual dysfunction, depression, and the impact of antidepressants. *J Clin Psychopharmacol* **29**:157–164.

Khin NA, Kronstein PD, Yang P, Ishida E, Hung HM, Mathis MV, *et al.* (2015). Regulatory and scientific issues in studies to evaluate sexual dysfunction in antidepressant drug trials. *J Clin Psychiatry* **76**:1060–1063.

Olivier B (2015). Serotonin: a never-ending story. *Eur J Pharmacol* **753**:2–18.

Oosting RS, Chan JS, Olivier B, Banerjee P, Choi YK, Tarazi F (2016). Differential effects of vilazodone versus citalopram and paroxetine on sexual behaviors and serotonin transporter and receptors in male rats. *Psychopharmacology (Berl)* **233**:1025–1034.

Osterberg L, Blaschke T (2005). Adherence to medication. *N Engl J Med* **353**:487–497.

Rosen RC, Lane RM, Menza M (1999). Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol* **19**:67–85.

Salonia A, Clementi MC, Ventimiglia E, Colicchia M, Capogrosso P, Castiglione F, *et al.* (2014). Prevalence and predictors of concomitant low sexual desire/interest and new-onset erectile dysfunction – a picture from the everyday clinical practice. *Andrology* **2**:702–708.