The Effect of Vortioxetine on Sexual Dysfunction in Adults With Major Depressive Disorder or Generalized Anxiety Disorder

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ABSTRACT

Introduction
Patients with major depressive disorder (MDD) and generalized anxiety disorder (GAD) often suffer from sexual dysfunction, and many current treatments impair overall sexual functioning. Vortioxetine, an antidepressant approved in 2013, has a multimodal mechanism of action, working via the direct modulation of receptor activity and inhibition of the serotonin transporter.[1] The receptor profile of vortioxetine, as well as available preclinical and clinical data, suggest limited impact on sexual functioning.

Objectives
To evaluate the incidence of treatment-emergent sexual dysfunction (TESD) in patients with MDD or GAD and no baseline sexual dysfunction after short-term treatment with vortioxetine 5 to 20 mg/day, duloxetine 60 mg, or placebo. The primary objective of this analysis was to confirm the similarity of vortioxetine to placebo. Secondary analyses include a prespecified comparison of vortioxetine and duloxetine.

Methodology
The Arizona Sexual Experience Scale (ASEX) was used to assess sexual function in 7 short-term studies, [6 studies in MDD: NCT00635219,* NCT01140906,* NCT01153009,* NCT00672620,* NCT01179516, and NCT01163266; 1 study in GAD: NCT00730691*] – 5 of which included duloxetine* – using the dichotomous method of McGahuey.[2] Noninferiority was evaluated using the common risk difference in TESD incidence rates between vortioxetine and placebo in patients who developed sexual dysfunction, with a clinically meaningful margin of 10%.

Results
In this analysis, nearly 30% of randomized patients had no baseline sexual dysfunction (placebo, 309/1088 [28.4%]; vortioxetine 5 to 20 mg, 580/1985 [29.2%]; duloxetine, 226/756 [29.9%]). Within this group, the pooled incidences of developing TESD at any timepoint in the study were placebo 32.0% (range, 24.7-46.7%), vortioxetine 5 to 20 mg 37.1% (21.9-60.0%), and duloxetine 48.2% (43.9-60.0%). Overall, TESD rates with vortioxetine 5 and 10 mg were similar to those with placebo, except for a higher rate for 10 mg in MDD Study NCT01163266. TESD rates with duloxetine were significantly greater than with placebo, confirming assay sensitivity. In the 5 studies with duloxetine, the rates for TESD with vortioxetine 5 to 20 mg were lower than with duloxetine, except in MDD Study NCT01140906, where a higher rate was observed with vortioxetine 15 and 20 mg.

The common risk difference estimates for developing TESD generally increased with vortioxetine dose (5 mg, –4.6%; 20 mg, 9.9%) compared with placebo. Vortioxetine 5 mg was noninferior to placebo, and TESD incidence rates for vortioxetine 10, 15, and 20 mg were not statistically significantly higher vs. placebo. Overall, the common risk difference from placebo for developing TESD was not statistically significantly different for vortioxetine 5 to 20 mg (4.2%, 95% CI –2.4; 10.7). Duloxetine had a statistically significantly higher common risk difference for TESD compared with placebo (15.0%, 95% CI 5.8; 24.1), with a statistically significantly lower risk noted for vortioxetine 5 mg (–22.0%, 95% CI –33.5; –10.6) and 10 mg (–19.6%, 95% CI –33.5; –5.7) relative to duloxetine. Subgroup (age, sex) results were generally consistent with overall results.

Conclusion
The risk of developing TESD for MDD or GAD patients without baseline sexual dysfunction was not statistically significantly different between vortioxetine doses (5-20 mg/day) and placebo, with noninferiority demonstrated at 5 mg. The risk of developing TESD was higher with duloxetine compared with placebo and vortioxetine 5 and 10 mg.

INTRODUCTION

- Despite clinical effectiveness, most of the currently available antidepressants produce sexual dysfunction in men and women and affect all aspects of sexual activity, decreasing desire, arousal, orgasm, and satisfaction. Such side effects affect the patient's quality of life, can lead to therapeutic noncompliance, and often interfere with recovery from a depressive episode.[3-6] Hu et al[7] determined that patients taking antidepressants ranked sexual dysfunction as the most bothersome adverse event (AE), followed by drowsiness/fatigue, weight gain, and insomnia.
- Vortioxetine is an antidepressant approved in doses from 5 mg to 20 mg/day for the treatment of adults with MDD.[8] Its mechanism of action is thought to combine a direct effect on receptor activity and serotonin (5-HT) reuptake inhibition.[9-11]
- In vitro studies in recombinant cell lines show that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and 5-HT transporter inhibitor.[9-11] Vortioxetine is thought to exert broad antidepressant activity with a low risk for TESD because of this unique multimodal mechanism of action.
- This analysis was designed to evaluate the incidence of TESD in MDD or GAD patients, treated with vortioxetine 5 to 20 mg/day, duloxetine 60 mg, or placebo for up to 8 weeks, who exhibited no baseline symptoms of sexual dysfunction as measured by the ASEX.
- The ASEX is a validated, self-administered questionnaire that prospectively measures the following 5 items relating to sexual functioning: sex drive, ease of arousal, ability to achieve erection (men)/lubrication (women), ease of reaching orgasm, and orgasm satisfaction. It is designed to identify and monitor TESD in individual patients.

OBJECTIVE

- The primary objective of the ASEX analyses was to evaluate the similarity of vortioxetine to placebo via a noninferiority hypothesis.
  - Noninferiority was evaluated by comparing the upper bound of the 2-sided 95% confidence interval (CI) for the difference in TESD incidence rates between vortioxetine and placebo in patients who developed sexual dysfunction at any time during the study period.
  - A clinically meaningful margin was set at 10 percentage points.[2]
- Prespecified secondary analyses were conducted to demonstrate that vortioxetine treatment results in significantly less TESD compared to duloxetine via a superiority hypothesis. Superiority was evaluated using the 2-sided 95% CI for the difference in TESD incidence rates between vortioxetine and duloxetine in patients who developed sexual dysfunction at any time during the study period.

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METHODS

- The ASEX was used to detect the emergence of sexual dysfunction in 7 randomized, controlled, short-term studies [6 studies in MDD: NCT00635219,* NCT01140906,* NCT01153009,* NCT00672620,* NCT01179516, and NCT01163266; 1 study in GAD: NCT00730691*], 5 of which included duloxetine*.
- The presence of sexual dysfunction based on ASEX scoring was determined using the following definition[2]:
  - A total ASEX score of ≥19, or
  - A score of ≥5 on any individual ASEX item, or
  - A score of ≥4 on 3 ASEX items.
- Various sensitivity analyses were conducted and evaluated for consistency with the TESD results, including incidence of TESD at 2 consecutive visits.
- Subgroup analyses were also conducted for age (≤50 years, >50 years) and gender.
- Impact of treatment on baseline sexual dysfunction status (normal, abnormal) for the change from baseline in ASEX total score and individual items was also assessed.
  - A shift in sexual function was defined for each individual item on the ASEX if the item changed from ≤3 to >3, from 4 to 5 or 6, or from 5 to 6 during the treatment period.
  - Worsening was defined for a patient with sexual dysfunction at baseline if the patient had ≥3 different items on the ASEX shift at the same visit.
- Comparisons for doses of vortioxetine 5 to 20 mg vs placebo and duloxetine were based on the estimated common risk difference and 95% CI using the Cochran-Mantel-Haenszel (CMH) method stratified by study.[9,11]
- All comparisons were conducted at the nominal 0.05 level of significance with no adjustment for multiple comparisons.
- The incidence of sexual dysfunction as a spontaneously reported treatment-emergent AE was assessed across the entire patient population of MDD and GAD studies.

RESULTS

Incidence of Sexual Dysfunction at Baseline

- Across all studies in which ASEX data were collected, approximately 30% of patients in each treatment group were without sexual dysfunction at baseline (placebo, 309/1088 patients [28.4%]; vortioxetine total group, 580/1985 patients [29.2%]; and duloxetine, 226/756 patients [29.9%]).
  - Sample sizes for placebo, each vortioxetine dose, and duloxetine were generally less than 50 patients per treatment arm in each study.

Incidence of TESD Across Clinical Trials

- The overall pooled incidence of TESD for patients receiving vortioxetine (37.1%) was slightly higher than that for placebo (32.0%). The incidence of TESD in duloxetine-treated patients was 48.2% (**Table 1**).

Table 1. Incidence of TESD in Patients Without Sexual Dysfunction at Baseline by Dose and Individual Study as Assessed by Shift in ASEX Status

Study	Incidence of Treatment-Emergent Sexual Dysfunction By Total Number of Patients in Each Treatment Arm – n (%)						
	Placebo (n=1088)	Vortioxetine 5 mg (n=465)	Vortioxetine 10 mg (n=616)	Vortioxetine 15 mg (n=449)	Vortioxetine 20 mg (n=455)	Vortioxetine Total (n=1985)	Duloxetine 60 mg (n=756)
NCT00635219 Incidence (%) Difference vs. Placebo Difference vs. Duloxetine	7/15 (46.7) – –	3/14 (21.4) -25.3 -38.6	10/21 (47.6) 0.9 -12.4	– – –	– – –	13/35 (37.1) -9.6 -22.9	9/15 (60.0) 13.3 –
NCT01140906 Incidence (%) Difference vs. Placebo Difference vs. Duloxetine	12/27 (44.4) – –	– – –	– – –	22/40 (55.0) 10.6 11.1	23/35 (65.7) 21.3 21.8	45/75 (60.0) 15.6 16.1	18/41 (43.9) -0.5 –
NCT00672620 Incidence (%) Difference vs. Placebo Difference vs. Duloxetine	14/42 (33.3) – –	18/48 (375) 4.2 -9.4	– – –	– – –	– – –	18/48 (375) 4.2 -9.4	23/49 (46.9) 21.2 –
NCT00730691 Incidence (%) Difference vs. Placebo Difference vs. Duloxetine	20/81 (24.7) – –	14/74 (18.9) -5.8 -27.0	19/77 (24.7) 0.0 -21.2	– – –	– – –	33/151 (21.9) -2.8 -24.0	34/74 (45.9) 13.6 –
NCT01153009 Incidence (%) Difference vs. Placebo Difference vs. Duloxetine	21/58 (36.2) – –	– – –	– – –	16/45 (35.6) -0.6 -17.6	16/45 (35.6) -0.6 -17.6	32/90 (35.6) -0.6 -17.6	25/47 (53.2) 17.0 –
NCT01163266 Incidence (%) Difference vs. Placebo Difference vs. Duloxetine	14/50 (28.0) – –	– – –	24/50 (48.0) 20.0 –	– – –	20/48 (41.7) 13.7 –	44/98 (44.9) 16.9 –	– – –
NCT01179516 Incidence (%) Difference vs. Placebo Difference vs. Duloxetine	11/36 (30.6) – –	– – –	14/42 (33.3) 2.7 –	16/41 (39.0) 8.4 –	– – –	30/83 (36.1) 5.5 –	– – –
All Studies Incidence (%) Difference vs. Placebo Difference vs. Duloxetine	99/309 (32.0) – –	35/136 (25.7) -6.3 -22.5	67/190 (35.3) 3.3 -12.9	54/126 (42.9) 10.9 -5.3	59/128 (46.1) 14.1 -2.1	215/580 (371) 5.1 -11.1	109/226 (48.2) 16.2 –

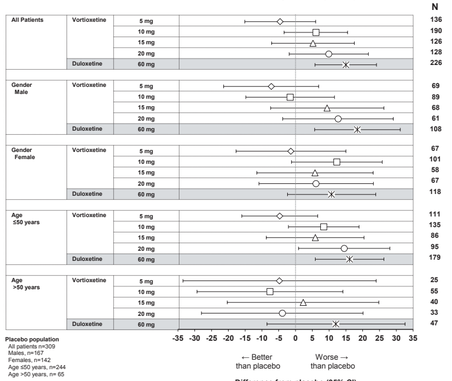
Negative change indicates improvement.

- TESD rates varied across the clinical studies in which the ASEX was utilized.
  - Placebo, 24.7% to 46.7%
  - Vortioxetine total group, 21.9% to 60.0%
  - Duloxetine, 43.9% to 60.0%
- The incidence of TESD increased with increasing vortioxetine dose (range: 5 mg, 25.7%; 20 mg, 46.1%), with the incidence for 5 mg being less than placebo.
- In the 5 studies that used duloxetine as an active reference, TESD rates for vortioxetine 5 to 20 mg were lower than for duloxetine, with the exception of one MDD study (NCT01140906), where higher incidence rates were noted for 15 and 20 mg.

Common Risk Difference for the Emergence of TESD in Patients Without Sexual Dysfunction at Baseline

- The risk of developing TESD in patients without sexual dysfunction at baseline in the MDD/GAD short-term pool, based on the analysis of the common risk difference, is presented in **Figure 1**.

Figure 1. Common Risk Difference of Developing Treatment-Emergent Sexual Dysfunction in Patients Without Sexual Dysfunction at Baseline in the MDD/GAD Short-Term Pool as Assessed by ASEX (CMH)

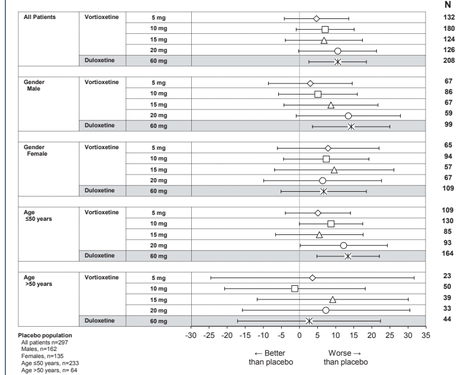


- For the range of vortioxetine doses (5 to 20 mg), estimates of the common risk difference from placebo for TESD incidence generally increased with increasing dose (range: 5 mg, –4.6%; 20 mg, 9.9%).
- The common risk difference for vortioxetine 5 mg was noninferior to placebo in incidence of TESD. While the 10, 15, and 20 mg doses did not meet the criteria for noninferiority, none were statistically significantly higher than placebo.
- Patients treated with duloxetine had statistically significantly higher TESD rates than those on placebo (estimated common risk difference, 15.0%) or on vortioxetine 5 or 10 mg (22.0% and 19.6%, respectively).
- Higher TESD rates were noted for female patients than for male patients and for patients >50 years old than for younger patients across all treatments.
- For male patients, estimates of the common risk difference from placebo for TESD incidence increased with increasing vortioxetine dose (range: 5 mg, –7.2%; 20 mg, 12.7%).
  - The TESD incidence for vortioxetine 5 mg was noninferior to placebo.
  - Vortioxetine 10, 15, and 20 mg did not meet the criteria for noninferiority to placebo; however, the incidence of TESD was not statistically significantly higher than placebo.
  - The TESD incidence for duloxetine was statistically significantly higher than for placebo and vortioxetine 5 mg (estimated common risk difference 18.4% and 23.9%, respectively).
- For female patients, estimates of the common risk difference from placebo for TESD incidence showed no dose trend with vortioxetine (5 mg, –1.4%; 10 mg, 12.3%; 15 mg, 5.8%; 20 mg, 6.1%).
  - None of the vortioxetine doses were noninferior to placebo; however, the incidence of TESD was not statistically significantly higher than placebo for any dose.
  - The TESD incidence for duloxetine was statistically significantly higher than for vortioxetine 5 and 10 mg (estimated common risk difference 19.1% and 26.3%, respectively).
- For patients aged ≤50 years, estimates of the common risk difference from placebo for the TESD incidence generally increased with increasing vortioxetine dose (range: 5 mg, –4.7%; 20 mg, 14.5%), with 20 mg being statistically significantly higher than placebo.
  - The TESD incidence for vortioxetine 5 mg was noninferior to that with placebo.
  - Neither vortioxetine 10 nor 15 mg met the criteria for noninferiority to placebo; however, the incidence of TESD was not statistically significantly higher than placebo.
  - The TESD incidence for duloxetine was statistically significantly higher than for placebo and vortioxetine (estimated common risk difference 16.1% and 17.6%, respectively).
- For patients >50 years, estimates of the common risk difference from placebo for TESD incidence showed no dose trend (range: 10 mg, –7.6%; 15 mg, 2.3%).
  - All vortioxetine doses were similar to placebo, although none were noninferior to placebo; however, the incidence of TESD was not statistically significantly higher than placebo for any dose.
  - The TESD incidence for duloxetine was statistically significantly higher than for vortioxetine 5 and 10 mg, and numerically higher than for placebo (estimated common risk difference 34.8%, 38.7%, and 12.0%, respectively).
  - Results for this subgroup are more limited given the smaller sample size for all treatments.

Incidence of TESD at 2 Consecutive Visits in Patients Without Sexual Dysfunction at Baseline

- The overall pooled incidence of TESD at 2 consecutive visits during treatment for patients receiving vortioxetine 5 to 20 mg doses (24.2%) was higher than placebo (16.5%) but lower than duloxetine (27.4%) (**Figure 2**).
- The rates of TESD at 2 consecutive visits varied across the studies for placebo (11.4% to 25.9%), vortioxetine 5 to 20 mg total group (14.6% to 35.1%), and duloxetine (19.5% to 40.0%).
  - Across the range of vortioxetine doses of 5 to 20 mg, the incidence increased with increasing dose (range: 5 mg, 18.9%; 20 mg, 31.7%).
- TESD rates at 2 consecutive visits for vortioxetine 5 to 20 mg were higher than for placebo in all studies, and were lower than for duloxetine in 4 of the 5 studies (except MDD Study NCT01140906: vortioxetine 15 mg, 30.0%; vortioxetine 20 mg, 41.2%; duloxetine, 19.5%).
  - Overall estimates of the common risk difference of vortioxetine 5 to 20 mg to placebo generally increased with increasing dose (range: 5 mg, 4.7%; 20 mg, 10.6%).
  - No vortioxetine dose was noninferior to placebo; however, none had TESD rates statistically significantly higher than placebo or duloxetine.
  - Duloxetine led to a statistically significantly higher TESD rate than placebo (estimated common risk difference, 10.6%).
- The subgroup results by gender and age were generally consistent with the overall results. Higher TESD rates at 2 consecutive visits were noted for female patients compared to male patients, and for patients aged older than 50 years compared to patients aged 50 years or less, across all treatments.

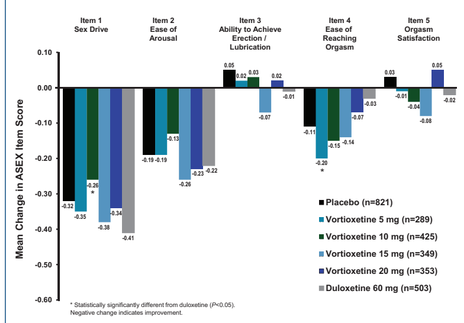
Figure 2. Common Risk Difference of Developing Treatment-Emergent Sexual Dysfunction at 2 Consecutive Visits in Patients Without Sexual Dysfunction at Baseline in the MDD/GAD Short-Term Pool as Assessed by ASEX (CMH)



ASEX Individual Items

- Improvements were noted for all treatment groups on all individual ASEX items, most notably item 1 (sex drive), item 2 (ease of arousal), and item 4 (ease of reaching orgasm), although no comparisons to placebo were statistically significant (*P*>0.05) (**Figure 3**).
- Slight worsening relative to baseline scores were observed for some groups, including placebo, for item 3 (ability to achieve erection [men]/lubrication [women]) and for item 5 (orgasm satisfaction).
- None of the vortioxetine doses or duloxetine showed statistically significant improvements over placebo on any individual item.

Figure 3. Mean Change in ASEX Individual Item Scores From Baseline to Week 8 in the MDD/GAD Short-Term Pool (MMRM)

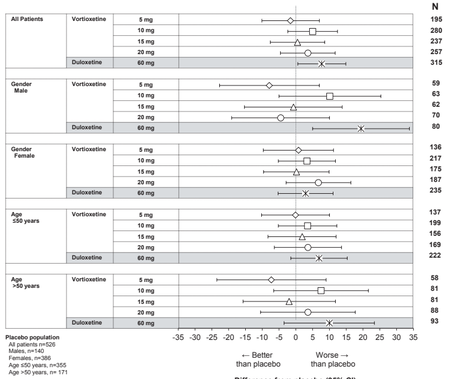


- Improvements from baseline to Week 8 in ASEX total score were noted for each gender and age group in all treatment groups, although no comparisons to placebo were statistically significant (*P*>0.05).
- Improvements from baseline were generally smaller for older than for younger patients across treatment groups.

Worsening of Sexual Dysfunction in Patients With Sexual Dysfunction at Baseline

- The overall pooled incidence of worsening sexual dysfunction during treatment for patients receiving vortioxetine 5 to 20 mg (30.0%, range: 20.5% to 45.2%) was similar to that for placebo (28.1%, range: 14.8% to 37.8%) (**Figure 4**).
  - Duloxetine had a worsening incidence of 36.5% (range: 30.3% to 50.0%).
  - Rates of worsening for vortioxetine 5 and 10 mg were lower than for duloxetine in corresponding studies; rates of worsening for vortioxetine 15 and 20 mg were similar to those for duloxetine, except in Study NCT01153009, where lower rates were noted for vortioxetine 15 mg than for duloxetine.
- No dose trend was noted for the estimates of the common risk difference from placebo across vortioxetine doses (range: 5 mg, –1.6%; 10 mg, 5.0%).
  - Rates of worsening for vortioxetine 5 and 15 mg were judged noninferior to placebo. While vortioxetine 10 and 20 mg did not meet the criteria for noninferiority, neither dose had rates of worsening sexual dysfunction statistically significantly higher than placebo.
- Duloxetine led to statistically significantly higher rates of worsening compared to placebo and vortioxetine 5 mg (estimated common risk difference: 7.7% and 12.5%, respectively).
  - The subgroup results for worsening ASEX results by gender and age were generally consistent with the overall results.

Figure 4. Common Risk Difference of Worsening of Sexual Dysfunction in Patients With Sexual Dysfunction at Baseline as Assessed by ASEX (CMH)



Analysis of Spontaneously Reported Treatment-Emergent Adverse Events

- The evaluation of spontaneously reported sexual dysfunction AEs was conducted across the entire pool of MDD and GAD studies (14 in total), with a total population of 3377 patients receiving vortioxetine 5 to 20 mg.
- In the total MDD/GAD short-term pool, the overall incidence of spontaneously reported sexual dysfunction as a treatment-emergent AE was low and was similar in the vortioxetine total and placebo groups (2.2% and 1.0%, respectively), with no dose-related increase in AEs observed among the individual vortioxetine treatment groups (**Table 2**).
- The majority of AEs were libido decreased, anorgasmia, and orgasm abnormal for both genders in the combined vortioxetine group, which was similar to findings with placebo.
  - All events were nonserious, with 4 patients (<0.1%) in the vortioxetine total group having events that led to discontinuation from the study: 2 in the 5 mg group (libido decreased in 1 patient, erectile dysfunction and loss of libido concurrently in 1 patient) and 1 each in the 15 mg (sexual dysfunction) and 20 mg dose groups (anorgasmia).
- In the duloxetine group, the AE incidence was 5.7%; an event of erectile dysfunction in 1 patient (0.1%) led to discontinuation from the study.

Table 2. Incidence of Spontaneously Reported Sexual Dysfunction Adverse Events by MedDRA Preferred Term in the MDD/GAD Short-Term Pool

	Sexual Dysfunction Adverse Events – n (%)						
	Placebo (n=2230)	Vortioxetine 5 mg (n=1466)	Vortioxetine 10 mg (n=1007)	Vortioxetine 15 mg (n=449)	Vortioxetine 20 mg (n=455)	Vortioxetine Total (n=3377)	Duloxetine 60 mg (n=907)
Sexual Dysfunction Adverse Events	23 (1.0)	30 (2.0)	25 (2.5)	7 (1.6)	12 (2.6)	74 (2.2)	52 (5.7)
Libido decreased	14 (0.6)	15 (1.0)	10 (1.0)	5 (1.1)	7 (1.5)	37 (1.1)	17 (1.9)
Orgasm abnormal	4 (0.2)	4 (0.3)	5 (0.5)	2 (0.4)	3 (0.7)	14 (0.4)	11 (1.2)
Anorgasmia	1 (<0.1)	3 (0.2)	5 (0.5)	1 (0.2)	2 (0.4)	11 (0.3)	10 (1.1)
Ejaculation delayed	2 (<0.1)	2 (0.1)	3 (0.3)	0	1 (0.2)	6 (0.2)	11 (1.2)
Loss of libido	0	4 (0.3)	2 (0.2)	0	0	6 (0.2)	1 (0.1)
Erectile dysfunction	3 (0.1)	2 (0.1)	3 (0.3)	0	0	5 (0.1)	13 (1.4)
Vulvovaginal dryness	0	0	3 (0.3)	0	0	3 (<0.1)	0
Ejaculation disorder	0	1 (<0.1)	0	0	1 (0.2)	2 (<0.1)	2 (0.2)
Sexual dysfunction	1 (<0.1)	0	1 (<0.1)	1 (0.2)	0	2 (<0.1)	2 (0.2)
Disturbance in sexual arousal	0	1 (<0.1)	0	0	0	1 (<0.1)	0
Orgasmic sensation decreased	1 (<0.1)	0	0	1 (0.2)	0	1 (<0.1)	0
Ejaculation failure	1 (<0.1)	0	0	0	0	0	2 (0.2)

CONCLUSIONS

- For MDD or GAD patients without sexual dysfunction at baseline who received vortioxetine 5 to 20 mg/day for 8 weeks, the risk of developing TESD was not statistically significantly higher than the risk with placebo, with noninferiority demonstrated for vortioxetine 5 mg.
- For these patients, the overall risk of developing TESD was statistically significantly higher with duloxetine compared with placebo and vortioxetine 5 and 10 mg.
- Vortioxetine does not appear to negatively affect sexual functioning in patients reporting no symptoms at baseline, as measured by the shift in ASEX status at any visit or at two consecutive visits.
- Compared to placebo, vortioxetine does not appear to worsen the symptoms of sexual dysfunction in those patients reporting impaired sexual functioning at baseline.
- In the short-term pooled data, the overall incidence of spontaneously reported sexual dysfunction as a treatment-emergent adverse event was similar in the vortioxetine total and placebo groups, with no observed dose-related increase in AEs.

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