Effect of Lurasidone on Sexual Function in Major Depressive Disorder Patients With Subthreshold Hypomanic Symptoms (Mixed Features): Results From a Placebo-Controlled Trial

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ABSTRACT

Objective: The aim of this secondary analysis was to evaluate whether treatment with lurasidone was associated with impairment in sexual functioning in major depressive disorder (MDD) patients with subthreshold hypomanic symptoms (mixed features).

Methods: Patients meeting *DSM-IV-TR* criteria for MDD, who presented with 2 or 3 protocol-specified manic symptoms, were randomized to 6 weeks of double-blind treatment with flexible doses of either lurasidone 20–60 mg/d (n = 109) or placebo (n = 100). The study was conducted between September 2011 and October 2014. Change in sexual functioning was assessed utilizing the 14-item self-report Changes in Sexual Functioning Questionnaire (CSFQ-14) administered at baseline and week 6 endpoint. Change from baseline to week 6 in depression severity was assessed utilizing the Montgomery-Asberg Depression Rating Scale (MADRS) total score, the primary efficacy endpoint.

Results: Lurasidone significantly reduced mean MADRS total scores at week 6 endpoint (−20.5 vs −13.0; $P < .001$). Treatment with lurasidone was associated with significant endpoint improvement in CSFQ total scores versus placebo (+5.1 vs +3.1; $P < .05$). Fewer patients treated with lurasidone versus placebo shifted from normal to abnormal sexual function. The proportion of patients with a baseline-to-endpoint shift from normal to abnormal sexual function was smaller for lurasidone versus placebo (1.9% vs 4.3%; CSFQ criteria) at study endpoint. Use of higher lurasidone doses was not associated with greater impairment in sexual functioning. No treatment-emergent adverse events related to sexual function were reported during lurasidone treatment.

Conclusions: In this secondary analysis of a placebo-controlled trial involving patients with MDD and mixed features, lurasidone was not associated with treatment-related sexual dysfunction. These findings were consistent across both structured assessments using a validated sexual functioning questionnaire (CSFQ) as well as adverse event reporting.

Trial Registration: ClinicalTrials.gov identifier: NCT01421134

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Major depressive disorder commonly presents with impairment in sexual function, with prevalence estimates among untreated patients ranging up to 85%.[1] Low sexual desire is the most common complaint among depressed patients, followed by arousal difficulties, while delay and/or inability to achieve orgasm is less frequently affected.[2–7]

Various risk factors have been reported to increase the probability of developing depression-related sexual dysfunction, most notably gender (female > male), age (older > younger), severity of depression, alcohol dependence, and the presence of chronic medical conditions (eg, diabetes and cardiovascular illness).[8–10]

Treatment-emergent onset (or worsening) of sexual dysfunction commonly occurs, in a dose-related fashion, with antidepressant therapy, most notably with selective serotonin reuptake inhibitor (SSRI) antidepressants.[1,11–14] The results of a meta-analysis found rates of treatment-emergent sexual dysfunction during antidepressant treatment that ranged from 25%–80%,[14] with higher rates consistently reported for women compared to men.[15–18] Sexual dysfunction also commonly occurs during treatment with both typical and atypical antipsychotics, with prevalence rates in the range of 20%–60%.[19] Sexual dysfunction is one of the most frequent reasons for nonadherence to antidepressant therapy, cited as a reason for discontinuation in approximately 25% of patients treated with an SSRI.[20–22]

In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*),[23] the diagnosis of a mixed affective episode can be characterized by a mixed features specifier. For patients with a primary diagnosis of major depressive disorder, clinicians may specify "mixed features" to note the presence of subthreshold hypomanic symptoms. Preliminary prevalence estimates suggest that major depression with mixed features occurs in at least 25% of major depressive episodes.[24–27]

Major depression with mixed features is a subtype of depression that is often severe, with an increased risk for recurrence, substance abuse, suicide attempts, and functional disability.[24,26,28] It is not currently known whether the presence of mixed features is associated with increased rates of sexual dysfunction when compared to depression in patients without mixed features.

Clinical Points

- Sexual dysfunction is commonly associated with SSRI and SNRI antidepressant treatment (worsening or new onset), which may lead to medication discontinuation or diminished quality of life.
- In a placebo-controlled trial involving patients with major depressive disorder and mixed features, lurasidone was not associated with sexual dysfunction, based on patient self-report using a structured questionnaire as well as adverse event reporting.

Lurasidone is a novel atypical antipsychotic which has a receptor binding profile that suggests low risk for sexual dysfunction. In addition to having high affinity (as an antagonist) for the dopamine D_2 and serotonin 5-HT_7 receptors, it also has high affinity (as an antagonist) for 5-HT_{2A} and 5-HT_{2C} receptors and moderate affinity (as a partial agonist) for 5-HT_{1A} receptors.[29]

In a placebo-controlled trial,[30] lurasidone was found to be an efficacious treatment for patients with major depressive disorder with subthreshold hypomanic features (mixed features). We report here the effect of lurasidone compared to placebo on sexual functioning in this study based on the standard 14-item self-report version of the Changes in Sexual Functioning Questionnaire (CSFQ-14).

METHODS

Data utilized in this secondary analysis are based on a study that evaluated the efficacy and safety of lurasidone for the treatment of patients with major depressive disorder presenting with subthreshold hypomanic symptoms (mixed features). Details of the design of the study are summarized elsewhere.[30] In brief, this was a randomized, double-blind, placebo-controlled, 6-week study that enrolled a total of 209 patients at 18 sites in the United States and 26 sites in Europe. Patients assigned to lurasidone received once-daily flexible dosing in the range of 20–60 mg/d. The study (ClinicalTrials.gov identifier: NCT01421134) was conducted between September 2011 and October 2014.

The diagnosis of major depressive disorder was confirmed with the Structured Clinical Interview for *DSM-IV* Disorders–Clinical Trials version,[31] modified to record the presence of subthreshold hypomanic symptoms (mixed features). The *DSM-5* mixed features specifier requires at least 3 manic/hypomanic symptoms, while the study analyzed here permitted patients with 2 or 3 such symptoms to enter. The permissible number of manic symptoms was limited to 3 to reduce the likelihood that patients with undiagnosed bipolar disorder would be enrolled in the study. Patients were required to have a total score ≥ 26 on the Montgomery-Asberg Depression Rating Scale (MADRS)[32] at both screening and baseline visits.

The study was approved by an institutional review board at each investigational site and was conducted in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use's Good Clinical Practice guidelines and with the ethical principles of the Declaration of Helsinki. Prior to study entry, all patients reviewed and signed an informed consent document explaining study procedures and potential risks.

Table 1. Baseline Demographic and Clinical Characteristics (Safety Population)

	Lurasidone (n = 109)		Placebo (n = 100)	
Characteristic	n	%	n	%
Male	36	33.0	28	28.0
Race				
White	94	86.2	86	86.0
Black/African-American	14	12.8	12	12.0
Other	1	0.9	2	2.0
	Mean	SD	Mean	SD
Age, y	43.6	12.1	46.4	12.0
Lifetime no. of MDD episodes	4.5	4.7	4.2	3.2
Duration of current episode, mo	3.7	2.8	3.3	2.6
Baseline scores				
MADRS total	33.2	4.3	33.3	4.0
CGI-S	4.5	0.6	4.6	0.6
CSFQ total[a]	35.5	10.9	34.1	9.5

[a]CSFQ scores at baseline were missing in 2 placebo patients and 1 lurasidone patient.
Abbreviations: CGI-S = Clinical Global Impression–Severity scale, CSFQ = Changes in Sexual Functioning Questionnaire, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.

Efficacy Assessments: Depression and Sexual Function

The primary efficacy endpoint in the study was change from baseline to week 6 endpoint in MADRS total score; the key secondary endpoint was change from baseline to week 6 endpoint in the Clinical Global Impression–Severity scale (CGI-S),[33] which rates overall illness severity on a 7-point scale. The CSFQ-14[34] was a secondary outcome measure that was administered at baseline and week 6 endpoint. The CSFQ-14[35] is a 14-item, gender-specific, self-report questionnaire (different versions for men and women), with each item scored on a 5-point scale. Possible CSFQ total scores range from 14 to 70, with lower scores indicating greater levels of sexual dysfunction. The CSFQ-14 has 5 subscales that assess the following domains: pleasure (item 1); desire/frequency (items 2 and 3); desire/interest (items 4, 5, and 6); arousal/excitement (items 7, 8, and 9); and orgasm/completion (items 11, 12, and 13). Items 10 (aroused and then lose interest) and 14 (painful orgasm) do not map onto a subdomain. Previous validation studies indicate that the threshold for sexual dysfunction on the CSFQ-14 is a total score ≤ 47 in males and ≤ 41 in females.[35] A 3-point increase in the CSFQ total score is considered to be a clinically meaningful improvement.[36]

Statistical Analysis

Since the CSFQ was prespecified as a safety outcome, the CSFQ analysis was conducted on the safety population, which consisted of all randomized patients who received at least 1 dose of study medication. An analysis of covariance

Table 2. Efficacy Measures: Change From Baseline to Week 6 Endpoint

	Lurasidone		Placebo		Treatment Difference (95% CI)	*P* Value	Effect Size
	n	Value	n	Value			
MADRS total							
Baseline mean (SD)	108	33.2 (4.3)	100	33.3 (4.0)	−7.5 (−10.2 to −4.8)	<.001	0.80
LS mean change (SE)[a]		−20.5 (1.0)		−13.0 (1.0)			
CGI-S							
Baseline mean (SD)	108	4.6 (0.6)	100	4.6 (0.6)	−0.6 (−1.0 to −0.3)	<.001	0.60
LS mean change (SE)[a]		−1.8 (0.1)		−1.2 (0.1)			
CSFQ total							
All patients							
Baseline mean (SD)[b]	108	35.4 (10.9)	98	34.1 (9.5)	2.0 (0.0 to 4.0)	.046	
LS mean change (SE)[c]	105	+5.1 (0.7)	96	+3.1 (0.7)			
Female patients							
Baseline mean (SD)	72	33.8 (10.9)	70	31.8 (8.9)	1.6 (−0.9 to 4.2)	.20	
LS mean change (SE)[c]	70	+5.1 (0.9)	69	+3.4 (1.0)			
Male patients							
Baseline mean (SD)	36	38.9 (10.1)	28	39.9 (8.4)	2.8 (−1.6 to 7.2)	.20	
LS mean change (SE)[c]	35	+4.8 (1.5)	28	+2.0 (1.5)			

[a]Significance values based on a mixed model for repeated-measures analysis.
[b]CSFQ scores at baseline were missing in 2 placebo patients and 1 lurasidone patient.
[c]Significance values based on analysis of covariance (last observation carried forward).
Abbreviations: CGI-S = Clinical Global Impression–Severity scale, CSFQ = Changes in Sexual Functioning Questionnaire, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale.

was performed on the CSFQ total and subscale scores using a last observation carried forward (LOCF) imputation approach. Cohen *d* effect size was calculated as the difference in the LS mean change score divided by the pooled standard deviation. Given the exploratory nature of the secondary safety variables, adjustments for multiple comparisons were not applied to these analyses.

Improvement in MADRS total score was evaluated on the intent-to-treat population, which consisted of randomized patients who received at least 1 dose of study medication and both baseline and at least 1 postbaseline MADRS or CGI-S assessment. Change from baseline in MADRS total score was assessed using a mixed model for repeated measures analysis including fixed effects for treatment, visit, and pooled center; baseline score as a covariate; and a treatment-by-visit interaction term. An unstructured covariance matrix was used for within-patient correlation.

Treatment response was defined as ≥ 50% reduction from baseline to week 6 endpoint in MADRS total score. Remission was defined as a week 6 endpoint MADRS total score ≤ 12.

A post hoc mediation analysis was performed, using the methodology of Baron and Kenny,[37] to evaluate the extent to which week 6 endpoint change in CSFQ total score either was a direct effect of lurasidone or was mediated by change in depression severity (the mediating variable).

RESULTS

The safety sample consisted of 209 patients, of whom 206 patients had a CSFQ assessment at baseline and were randomly assigned to a treatment group. Baseline characteristics were approximately similar for both the lurasidone and placebo treatment groups (Table 1). A similarly high proportion of female (84.5%) and male (81.2%) patients met established CSFQ criteria for sexual dysfunction at baseline. Baseline severity of sexual dysfunction was not correlated with baseline depression severity (Pearson correlation, MADRS vs CSFQ, $r = -0.051$).

The mean daily dose of lurasidone during the study was 36.2 mg; the modal daily dose of lurasidone was 20 mg for 32% of patients, 40 mg for 29%, and 60 mg for 39%. Study completion rates were high in both the lurasidone group (93.6%) and the placebo group (85.3%).

As previously reported,[30] the least squares mean change from baseline to week 6 endpoint was significantly greater for lurasidone versus placebo for the MADRS total score (primary endpoint; −20.5 vs −13.0; $P < .001$) and for the CGI-S (key secondary endpoint; −1.8 vs −1.2; $P < .001$; Table 2). In addition, a significantly higher proportion of patients treated with lurasidone versus placebo met week 6 endpoint criteria for response (64.8% vs 30.0%; $P < .001$; LOCF) and remission (49.1% vs 23.0%; $P < .001$; LOCF).

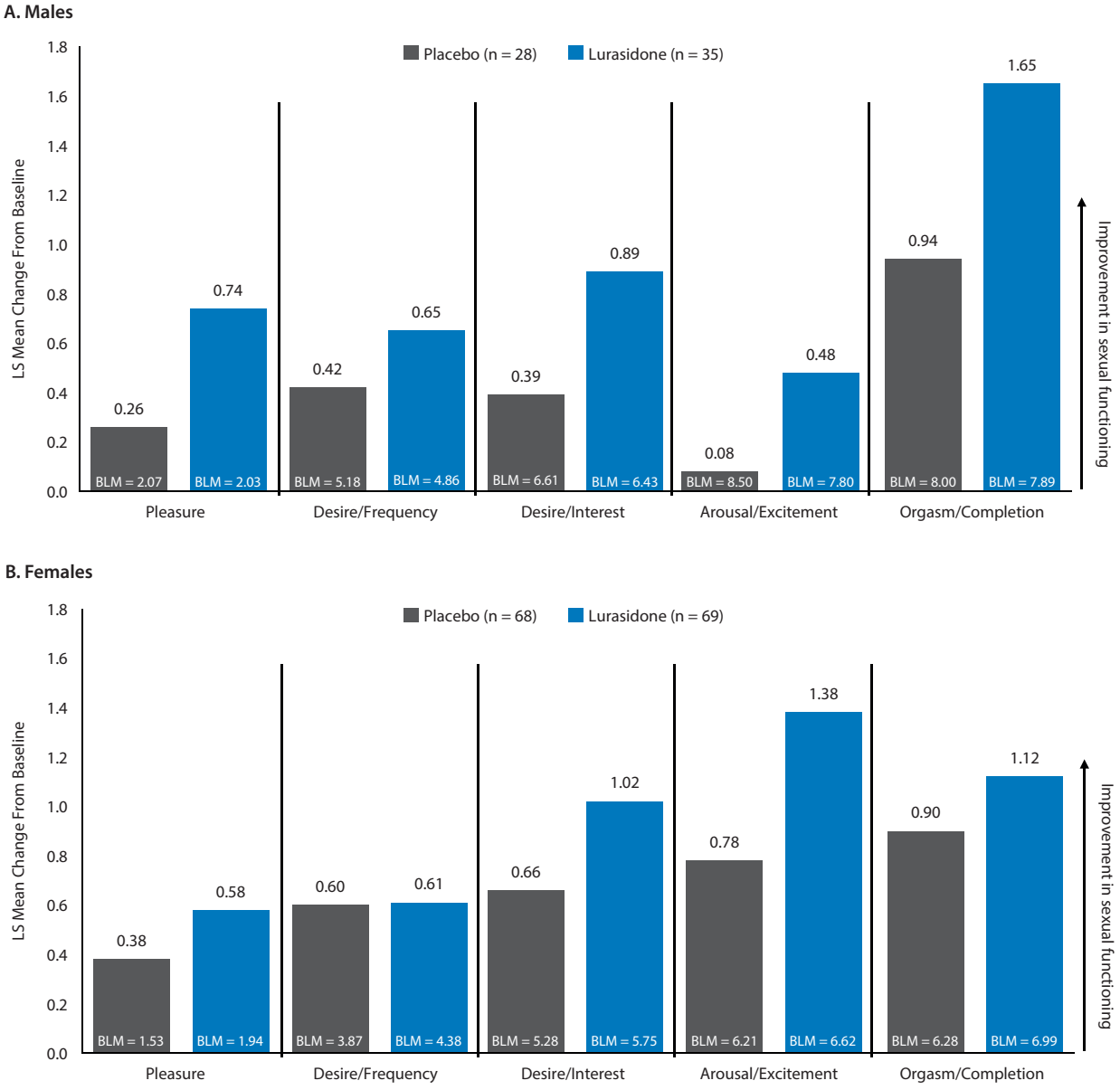
Mean change from baseline to week 6 endpoint in the CSFQ total score significantly favored lurasidone versus placebo (+5.1 vs +3.1; $P = .046$; Table 2). Treatment with lurasidone was associated with numerically greater week 6 endpoint improvement in the CSFQ total score in patients who met responder (CSFQ, +5.0) and remitter (CSFQ, +5.6) criteria, compared with patients who did not meet responder criteria (CSFQ, +3.6).

Effect of Gender and Age on CSFQ Change

Change from baseline to week 6 endpoint in the CSFQ total score for lurasidone and placebo was +5.1 vs +3.1 (effect size, 0.22) for women and +4.8 vs +2.0 (effect size, 0.33) for men (Table 2).

Among male patients, treatment with lurasidone was associated with numerically greater improvement in all 5 CSFQ subscale scores, with effect sizes ranging from 0.12 to 0.49 (Figure 1A). Among female patients, a similar numerical treatment advantage was observed in favor of lurasidone in

Figure 1. Endpoint Change in CSFQ Subscale Scores



Abbreviations: BLM = baseline mean, CSFQ = Changes in Sexual Functioning Questionnaire, ES = effect size, LS = least squares.

4 of 5 CSFQ subscales (Figure 1B); no treatment effect was observed in the CSFQ desire/frequency subscale in females.

Week 6 endpoint change in the CSFQ total score for lurasidone versus placebo was similar for older (age > 45 years: +5.9 vs +3.8) and younger (age < 45 years: +4.7 vs +2.1) patients.

Effect of Lurasidone Dose on CSFQ Change

Week 6 endpoint change in CSFQ total score for lurasidone, adjusted for baseline MADRS total score as a covariate, was similar for the 20 mg/d, 40 mg/d, and 60 mg/d doses, respectively, on an observed case analysis (+3.0, +3.5. +4.4) and an LOCF endpoint analysis (+3.3, +3.7, +4.4).

Effect of Baseline Sexual Dysfunction on CSFQ Change

Among patients (n = 172) meeting CSFQ criteria for sexual dysfunction at baseline, improvement in CSFQ total score on lurasidone was nonsignificantly greater than on placebo at LOCF endpoint (+5.7 vs +3.8; $P = .069$).

A smaller proportion of patients treated with lurasidone compared with placebo shifted sexual functioning status from normal at baseline to abnormal at endpoint for all subjects (1.9% vs 4.2%), for males (2.9% vs 7.1%), and for females (1.4% vs 2.9%).

Mediation Analysis

The post hoc mediation analysis found a significant effect for the relationship between treatment with lurasidone and

improvement in MADRS total score (β = −0.335, $P < .001$) and a similarly significant effect for the relationship between improvement in MADRS total score and improvement in CSFQ total score (β = −0.366, $P < .001$). The direct effect of lurasidone on endpoint change in CSFQ total score was negligible, suggesting that the observed change in CSFQ total score was largely due to an indirect effect of lurasidone on improvement in MADRS total score.

Adverse Events

There were 2 treatment-emergent adverse events related to sexual function, both of which were reported by 1 patient each in the placebo treatment group (loss of libido and sexual dysfunction). No adverse events related to sexual function were spontaneously reported in the lurasidone treatment group.

Prolactin Levels

Mean baseline prolactin levels for males and females were 16.0 ng/mL and 10.1 ng/mL, respectively, in the lurasidone group and 14.3 ng/mL and 6.0 ng/mL, respectively, in the placebo group. Treatment with lurasidone vs placebo was associated with a median change in prolactin at endpoint of +2.5 vs −0.3 ng/mL in females and −0.1 vs +0.3 ng/mL in males.

DISCUSSION

Sexual dysfunction occurs in up to 85% of patients with a diagnosis of major depressive disorder (MDD).[1] Antidepressant treatment, particularly SSRI and serotonin-norepinephrine reuptake inhibitor (SNRI) agents, but also selected atypical antipsychotics, may induce dose-related sexual dysfunction at rates ranging up to 50% of patients or higher.[15–22]

Results of the secondary and post hoc analyses summarized here provide several lines of evidence indicating that treatment with lurasidone is associated with low risk for sexual dysfunction. First, significant improvement in sexual functioning, as measured by endpoint change in the CSFQ total score, was observed on lurasidone compared with placebo in the study population. Second, the proportion of patients with a baseline-to-endpoint shift from normal to abnormal sexual function was smaller for lurasidone compared to placebo (1.9% vs 4.3%; based on CSFQ criteria[35]). Third, no treatment-emergent adverse events related to sexual function were spontaneously reported during lurasidone treatment. Fourth, a post hoc mediational analysis found no direct negative (or positive) effect of lurasidone on sexual functioning; change in CSFQ total score was significantly mediated by change in MADRS total score ($P < .001$). This finding was further supported by results of a post hoc analysis that found stepwise increases in mean CSFQ improvement scores for patients who achieved endpoint improvement (but not response) on the MADRS total score and patients who were endpoint responders and remitters. Finally, use of higher lurasidone doses was not associated with greater impairment in sexual functioning. If sexual dysfunction were a pharmacologic effect of lurasidone therapy, one would expect higher doses to be associated with higher rates of sexual dysfunction.

It is notable that sexual dysfunction, in this MDD with mixed features population, occurred in 83% of patients at baseline, a rate that was at the higher end of the range previously reported for patients with unipolar depression without mixed features.[1] The high rate of sexual dysfunction observed at baseline in the current study may be related to several factors, including the greater severity of depression in the current treatment sample (mean baseline MADRS score = 33) and the mixed features depression diagnosis (rates of sexual dysfunction have not been established for this diagnostic subtype). Recent treatment with an SSRI or SNRI antidepressant may have also contributed to the high rate of sexual dysfunction; however, patients were required to have discontinued antidepressants for at least 10 days prior to baseline (21 days for fluoxetine), which likely limited the potential for any confounding effects of prior antidepressant use on sexual function in this study.

Treatment-emergent sexual dysfunction has been reported in meta-analyses of both SSRI and SNRI antidepressants (25%–80%)[14] and atypical antipsychotics (20%–60%; data reflect treatment of patients with depression and schizophrenia).[19] In contrast to these results, a pooled analysis of adjunctive therapy with aripiprazole for MDD found modest but significant improvement in sexual functioning in women (but not men) after controlling for level of improvement in depression symptom severity.[38] In addition, in an open-label, community-based study of patients with a diagnosis of schizophrenia, treatment with aripiprazole demonstrated modest but significant improvement in sexual function compared to treatment with olanzapine, quetiapine, or risperidone.[39]

Among patients with MDD, female sex has been reported to be a risk factor for treatment-emergent sexual dysfunction; pretreatment rates of sexual dysfunction are also higher in women with MDD compared to men.[8,15–18] Similar findings were observed in the current study. Females presented with lower CSFQ scores at pretreatment baseline (indicating greater sexual dysfunction) and demonstrated somewhat less improvement in sexual functioning compared with males during study treatment. Previous research has reported a correlation between increased levels of prolactin and sexual dysfunction.[40] The lack of effect of lurasidone on prolactin in both men and women in this study is consistent with the absence of sexual dysfunction observed with lurasidone treatment in this study.

Among patients with MDD, older age has also been reported to be a risk factor for treatment-emergent sexual dysfunction.[8,15] In the current study, comparable levels of improvement in sexual functioning were observed for patients above and below 45 years of age.

Normal sexual functioning depends on the interplay of neurotransmitter systems, including serotonin, dopamine, nitric oxide, acetylcholine, GABA, and norepinephrine.[41–43]

Adding to the complexity of the underlying neural activity is evidence indicating that serotonin and dopamine receptor subtypes may be associated with differential positive or negative effects on sexual function. Lurasidone has some mechanistic similarities with medications used to ameliorate sexual dysfunction (eg, agents with potent 5-HT_{2A} antagonist and 5-HT_{1A} partial agonist effects)[44–49] and lacks serotonin reuptake inhibiting properties that can exacerbate sexual dysfunction. It is possible that current findings may be attributable to these mechanistic considerations.

Limitations of the current study include the short study duration (6 weeks), the secondary nature of the analysis, and the absence of multiplicity correction for the CSFQ analysis. The dose range of lurasidone (20–60 mg/d) utilized in this study makes it uncertain whether the current results generalize to higher doses of lurasidone. Further study is needed to determine whether the current results extend to patients with non-mixed forms of MDD or other diagnoses for which lurasidone may be utilized.

In conclusion, lurasidone was not associated with treatment-related sexual dysfunction in this secondary analysis of a placebo-controlled trial involving patients with MDD and mixed features. These findings were consistent across both structured assessments using a validated sexual functioning questionnaire (CSFQ) as well as adverse event reporting.

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