Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study

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Objective: Accumulating evidence indicates that manic symptoms below the threshold for hypomania (mixed features) are common in individuals with major depressive disorder. This form of depression is often severe and is associated with an increased risk for recurrence, suicide attempts, substance abuse, and functional disability. This study evaluated the efficacy and safety of lurasidone in major depressive disorder with mixed features.

Methods: Patients meeting DSM-IV-TR criteria for major depressive disorder who presented with two or three protocol-defined manic symptoms were randomly assigned to 6 weeks of double-blind treatment with either lurasidone at 20–60 mg/day (N=109) or placebo (N=100). Changes from baseline in Montgomery-Åsberg Depression Rating Scale score (MADRS; primary outcome measure) and Clinical Global Impressions severity subscale score (CGI-S; key secondary outcome measure) were evaluated using a mixed model for repeated-measures analysis.

Results: Lurasidone significantly improved depressive symptoms and overall illness severity, assessed by least squares mean change at week 6 in the MADRS and CGI-S scores: −20.5 compared with −13.0 (effect size, 0.80) and −1.8 compared with −1.2 (effect size, 0.60), respectively. Significant improvement in manic symptoms, assessed by the Young Mania Rating Scale, was also observed, in addition to other secondary efficacy endpoints. Rates of discontinuation due to adverse events were low. The most common adverse events were nausea (6.4% and 2.0% in the lurasidone and placebo groups, respectively) and somnolence (5.5% and 1.0%).

Conclusions: Lurasidone was effective and well tolerated in this study involving patients with major depressive disorder associated with subthreshold hypomanic symptoms (mixed features).

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Accumulating evidence from epidemiological (1–3) as well as retrospective and prospective clinical studies (4–11) suggests that patients with major depressive disorder commonly present with manic symptoms below the threshold for hypomania (mixed features). Most prevalence estimates range from 25% to 45%, depending in part on how the population studied was defined, including the number and duration of manic symptoms. While rigorous comparisons are not available, a substantial body of evidence suggests that major depressive disorder with mixed features, in contrast to pure major depression, is characterized by greater illness severity (11, 12), increased frequency of depressive episode recurrence (2, 11), increased risk of suicide attempt (2, 8, 12–14), comorbid anxiety disorder (2, 8, 12) and substance abuse (2, 8, 12), greater functional disability (2, 12, 15), and poorer prognosis (12, 14). Given developments in the understanding of the prevalence of this clinical presentation, as well as its

distinct course and prognosis, DSM-5 incorporated a new "mixed features" specifier that may be used to recognize the presence of subthreshold symptoms of the opposite pole in patients presenting with either depressive or manic episodes.

No controlled trials to date have investigated the efficacy of any psychotropic agent in the treatment of major depressive disorder with mixed features. While standard antidepressants are widely used in the treatment of major depressive disorder, the efficacy and safety of these agents in patients with mixed features has not been established and is not well understood. However, multiple clinical reports suggest that standard antidepressants may be ineffective for this condition and may be associated with potential treatment-related complications, including suicidal ideation and behavior, manic switch, agitation, and impulsivity (14, 16–19). Although atypical antipsychotic agents and mood stabilizers have been suggested as treatment alternatives (20, 21), there is little experimental

evidence to support these clinical recommendations. Given the limitations of current treatment approaches, as well as the complex course and poor outcomes associated with this form of major depressive disorder, there is a pressing need for evidence-based treatments for this condition.

Lurasidone is an atypical antipsychotic agent with high affinity for D_2, 5-HT$_{2A}$, and 5-HT$_7$ receptors (Ki=1 nM, 0.5 nM, and 0.495 nM, respectively) (22). In animal models, the antidepressant effect of lurasidone has been shown to be mediated in part by antagonist activity at the 5-HT$_7$ receptor (23, 24). Atypical antipsychotics have been shown to have mood-stabilizing properties, and selected agents have demonstrated antidepressant efficacy in bipolar depression (20). Lurasidone has demonstrated efficacy in the treatment of bipolar depression, both as a monotherapy and as an adjunctive therapy with lithium or valproate (25, 26). Given this range of clinical effects, we hypothesized that lurasidone may be useful for the treatment of mixed forms of major depression.

The purpose of this study was to evaluate the efficacy and safety of lurasidone for the treatment of patients with major depressive disorder presenting with subthreshold hypomanic symptoms (mixed features).

METHOD

Patients

This multiregional study enrolled outpatients 18–75 years of age with a diagnosis of major depressive disorder based on DSM-IV-TR criteria, which was confirmed with the Structured Clinical Interview for DSM-IV Disorders–Clinical Trial version, modified to record the presence of mixed symptoms (27) and administered by an experienced and qualified rater. Patients were required to have a current major depressive episode, with a score ≥26 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (28) at both screening and baseline visits. In addition, patients were required to have two or three of the following manic symptoms, on most days for at least 2 weeks prior to screening: elevated or expansive mood, inflated self-esteem or grandiosity, more talkative than usual or pressure to keep talking, flight of ideas or racing thoughts, increased energy, increased or excessive involvement in activities with a high potential for negative consequences, and decreased need for sleep. Patients presenting with irritability, distractibility, and psychomotor agitation could be enrolled; however, consistent with DSM-5, these nonspecific symptoms were not included in the list of eligible manic symptoms required for study entry. External clinical reviewers verified the diagnoses of all study participants, based on audio recordings of diagnostic interviews conducted by site-based investigators.

The study was approved by an institutional review board at each investigational site and was conducted in accordance with the International Conference on Harmonisation 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. An independent data and safety monitoring board reviewed and monitored patient data throughout the study.

Study Design

This randomized, double-blind, placebo-controlled, flexible-dose study enrolled a total of 211 patients at 18 sites in the United States (N=62 patients) and 26 sites in Europe (N=149 patients) between September 2011 and October 2014.

After a washout period of at least 3 days, patients were randomly assigned, in a 1:1 ratio via an interactive voice/web response system, to receive 6 weeks of treatment with lurasidone or placebo. Study medication was provided in blister packs as identically matched tablets containing placebo or 20 mg or 40 mg of lurasidone. A central randomization center used a computer-generated list of random numbers to allocate study treatments. None of the investigators, study staff or patients had access to the randomization codes or list. Study medication was taken once daily in the evening with a meal or within 30 minutes after eating. Patients assigned to receive lurasidone were treated with 20 mg/day for days 1–7. Patients were dosed flexibly, in the range of 20–60 mg/day, starting on day 8.

Concomitant Medications

Treatment with anticholinergic agents, propranolol, or amantadine was permitted as needed (but not prophylactically) for movement disorders. Lorazepam, temazepam, or zolpidem (or their equivalent) were permitted during screening and weeks 1–3, as needed for anxiety or insomnia.

Efficacy Assessments

The primary efficacy endpoint was mean change from baseline to week 6 in MADRS total score. The key secondary efficacy endpoint (corrected for multiplicity) was mean change from baseline to week 6 in Clinical Global Impressions severity subscale score (CGI-S), which rates overall illness severity on a 7-point scale (29). Standard a priori criteria were employed for treatment response (≥50% reduction from baseline in MADRS score) and remission (MADRS score ≤12). Additional secondary efficacy assessments included the Young Mania Rating Scale (YMRS) (30), the Hamilton Anxiety Rating Scale (HAM-A) (31), and the Sheehan Disability Scale (32).

Safety and Tolerability Evaluations

Safety and tolerability assessments included incidence and severity of adverse events; the Simpson-Angus Rating Scale, the Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Rating Scale to evaluate movement disorders; and vital signs, laboratory tests, 12-lead ECG, and physical examination. Suicidal ideation and behavior were assessed using the Columbia–Suicide Severity Rating Scale (33). Treatment-emergent mania was defined, a priori, as a YMRS score ≥16 on any two consecutive assessments or at the final assessment, or an adverse event of mania or hypomania. Sexual functioning was assessed using the 14-item Changes in Sexual Functioning Questionnaire (34); total scores ≤47 for men and ≤41 for women

TABLE 1. Baseline Demographic and Clinical Characteristics in a Study of Lurasidone For the Treatment of Major Depressive Disorder With Mixed Features (Safety Population)

Characteristic	Lurasidone (N=109)		Placebo (N=100)	
	N	%	N	%
Male	36	33.0	28	28.0
Race				
White	94	86.2	86	86.0
Black or African American	14	12.8	12	12.0
Other	1	0.9	2	2.0
Region				
Europe	75	68.8	74	74.0
United States	34	31.2	26	26.0
Current number of manic symptoms				
Two	68	62.4	63	63.0
Three	41	37.6	37	37.0
History of at least one psychiatric hospitalization	52	47.7	55	55.0
	Mean	SD	Mean	SD
Age (years)	43.6	12.1	46.4	12.0
Major depressive episodes				
Lifetime number	4.5	4.7	4.2	3.2
Lifetime number with mixed features	2.5	3.8	2.3	2.5
Duration of current episode (months)	3.7	2.8	3.3	2.6
Duration of mixed features (months)	2.8	2.9	2.4	2.9
Montgomery-Åsberg Depression Rating Scale	33.2	4.3	33.3	4.0
Clinical Global Impressions severity subscale	4.5	0.6	4.6	0.6
Young Mania Rating Scale	11.1	4.5	10.3	4.4
Hamilton Rating Scale for Anxiety	17.0	6.6	16.9	6.2
Sheehan Disability Scale	20.0	5.0	20.5	5.1

indicate sexual dysfunction, and higher scores are associated with adequate sexual functioning.

Statistical Analysis

The safety population included all patients who were randomized and received at least one dose of study medication. The intent-to-treat population consisted of randomized patients who received at least one dose of study medication and had at least one postbaseline MADRS or CGI-S assessment. The primary (MADRS) and key secondary (CGI-S) efficacy endpoints, as well as the YMRS, were 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. In the analysis of the MADRS and CGI-S, a sequential testing procedure was used to control overall type I error at 5%.

Changes from baseline in secondary efficacy measures (HAM-A, Sheehan Disability Scale) were evaluated using an analysis of covariance (ANCOVA) model (including terms for treatment, pooled center, and baseline score) using last observation carried forward. Inferential analysis of secondary efficacy endpoints was not corrected for multiplicity. Effect sizes (Cohen's d) were calculated as the least squares mean

difference in the change score divided by the pooled standard deviation. The number needed to treat to achieve response (based on prespecified MADRS criteria) was calculated by assessing the reciprocal of the difference in responder rates in the lurasidone and placebo groups (35); the number needed to harm for selected adverse events was calculated by assessing the reciprocal of the difference in adverse effect rates for the lurasidone and placebo groups (35). Likelihood of being helped or harmed (the ratio of number needed to harm to number needed to treat) was calculated to illustrate trade-offs between benefits (response) and harms (incidence of individual adverse events and of an increase ≥7% in body weight [35]).

The estimated sample size of 100 patients per treatment group (adjusted for attrition) was determined based on a two-sample t test and was powered at 80% to detect a 4.5-point difference at week 6 in MADRS change scores for lurasidone compared with placebo, with a common standard deviation of 10.

RESULTS

Baseline Characteristics and Patient Disposition

A total of 327 patients were screened, of whom 211 (64.5%) were randomly assigned to 6 weeks of double-blind treatment (see Figure S1 in the data supplement that accompanies the online edition of this article). Of these, 209 patients (lurasidone, N=109; placebo, N=100) received at least one dose of study medication and comprised the safety population, of whom 208 comprised the intent-to-treat population used in all efficacy analyses. Study completion rates were high in both the lurasidone group (93.6%) and the placebo group (85.3%) (see Figure S1). 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%.

Baseline demographic and clinical characteristics were similar for the lurasidone and placebo groups (Table 1). The mean reported lifetime number of prior major depressive episodes was 4.3. The mean duration of the index depressive episode was 3.5 months, and of subthreshold hypomanic symptoms (mixed features) prior to screening, 2.6 months. A total of two protocol-specified manic symptoms were present in 130 patients (62.5%), and three symptoms in 78 patients (37.5%). The proportion of patients reporting specific manic symptoms at baseline was as follows: flight of ideas/racing thoughts, 66.8%; pressured speech, 61.1%; decreased need for sleep, 40.8%; increased energy/activity, 28.0%; elevated/expansive mood, 18.0%; increased/excessive involvement in pleasurable activities, 15.6%; and inflated self-esteem/grandiosity, 6.6%. The "nonspecific" symptoms of irritability, distractibility, and psychomotor agitation were reported at baseline by 57.3%, 59.2%, and 36.5% of patients, respectively.

Efficacy

The least squares mean change from baseline to week 6 in the MADRS total score (primary endpoint) was significantly greater for lurasidone compared with placebo (−20.5 and −13.0, respectively; p<0.001; effect size, 0.80) (Table 2). Least squares

TABLE 2. Change in Efficacy Endpoints at Week 6 in a Study of Lurasidone For the Treatment of Major Depressive Disorder With Mixed Features (Intent-to-Treat Population)

Measure	Lurasidone (N=108)				Placebo (N=100)				Treatment Difference	95% CI	p	Effect Size
	Baseline Mean	SD	LSM[a] Change	SE	Baseline Mean	SD	LSM[a] Change	SE				
Montgomery-Åsberg Depression Rating Scale[b]	33.2	4.3	−20.5	1.0	33.3	4.0	−13.0	1.0	−7.5	−10.2, −4.8	<0.001	0.80
Clinical Global Impressions severity subscale[b]	4.6	0.6	−1.8	0.1	4.6	0.6	−1.2	0.1	−0.65	−0.96, −0.34	<0.001	0.60
Young Mania Rating Scale[b]	11.1	4.6	−7.0	0.4	10.3	4.4	−4.9	0.4	−2.1	−3.1, −1.1	<0.001	0.61
Hamilton Rating Scale for Anxiety[c]	17.0	6.6	−9.9	0.6	16.9	6.2	−5.4	0.6	−4.5	−6.1, −2.9	<0.001	0.78
Sheehan Disability Scale[c]	20.0	5.0	−11.2	0.9	20.5	5.1	−6.4	0.9	−4.8	−7.2, −2.4	<0.001	0.68

[a] LSM=least squares mean.
[b] Significance values based on mixed model for repeated-measures analyses.
[c] Significance values based on analysis of covariance (last observation carried forward).

mean change at week 6 in the CGI-S score (key secondary endpoint) was also significantly greater for lurasidone compared with placebo (−1.8 and −1.2, respectively; p<0.001; effect size, 0.60) (Table 2). Statistical superiority compared with placebo was observed from week 1 through week 6 for the MADRS and from week 2 though week 6 for the CGI-S (Figure 1).

With respect to the MADRS, there was no statistically significant treatment interaction with gender, age, or geographic region. At week 6, significantly greater improvement in the MADRS total score was observed in the two geographic regions where the study was conducted, the United States (N=59; p<0.01; effect size, 0.78) and Europe (N=149; p<0.001; effect size, 0.92).

A significantly higher proportion of patients in the lurasidone group than in the placebo group met a priori response and remission criteria at week 6 (response: 64.8% compared with 30.0%; p<0.001; number needed to treat=3 [last observation carried forward]; remission: 49.1% compared with 23.0%; p<0.001; number needed to treat=4 [last observation carried forward]).

Lurasidone was associated with significantly greater least squares mean change at week 6 compared with placebo on the YMRS (−7.0 compared with −4.9; p<0.001; last observation carried forward), the HAM-A (−9.9 compared with −5.4; p<0.001), and the Sheehan Disability Scale (−11.2 compared with −6.4; p<0.001; last observation carried forward) (Table 2).

Change in MADRS score was assessed on an exploratory basis for patients with two compared with three protocol-specified manic symptoms at study baseline. Least squares mean change in MADRS score from baseline to week 6 was significantly greater with lurasidone than placebo for both patient subgroups. For patients with two manic symptoms, the change in MADRS score with lurasidone was −20.7, compared with −11.5 with placebo (p<0.001; effect size, 0.98); for patients with three manic symptoms, the change in MADRS score with lurasidone was −20.0 compared with −15.3 with placebo (p=0.038; effect size, 0.50).

Safety
Treatment-emergent adverse events reported with an incidence ≥2% in the lurasidone group, and more frequently

FIGURE 1. Least Squares Mean Change From Baseline in Efficacy Measures in a Study of Lurasidone For the Treatment of Major Depressive Disorder With Mixed Features[a]

A. Montgomery-Åsberg Depression Rating Scale Total Score
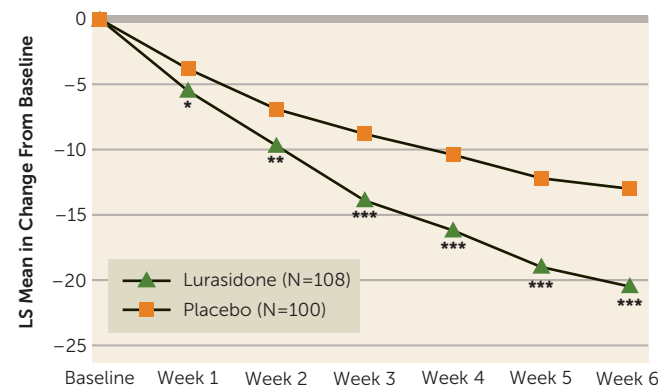
B. Clinical Global Impressions Severity Subscale
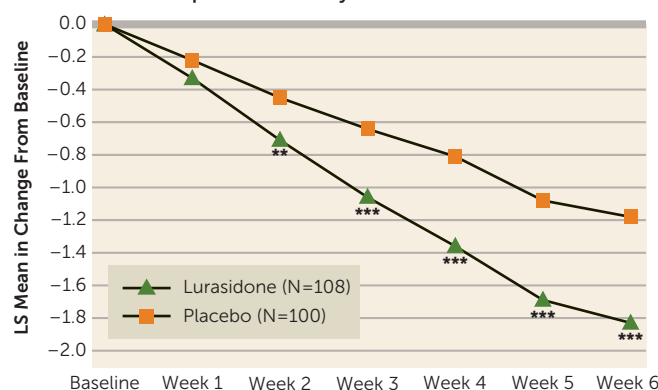
[a] Mixed model for repeated-measures analyses, intent-to-treat population. Effect sizes were 0.8 for the Montgomery-Åsberg Depression Rating Scale (primary efficacy endpoint) and 0.6 for the Clinical Global Impressions severity subscale (secondary efficacy endpoint).
*p<0.05. **p<0.01. ***p<0.001.

than in the placebo group, were nausea, somnolence, dizziness, akathisia, abdominal discomfort, dry mouth, and parkinsonism (Table 3). Number needed to harm was 23 for the two treatment-emergent adverse events with an incidence >5% (nausea and somnolence). There were no deaths in the

TABLE 3. Safety and Tolerability Parameters: Adverse Events in a Study of Lurasidone For the Treatment of Major Depressive Disorder With Mixed Features (Safety Population)[a]

Event	Lurasidone (N=109)		Placebo (N=100)	
	N	%	N	%
At least one event	44	40.4	38	38.0
Nausea	7	6.4	2	2.0
Somnolence[b]	6	5.5	1	1.0
Dizziness	4	3.7	3	3.0
Akathisia	4	3.7	2	2.0
Abdominal discomfort	4	3.7	1	1.0
Dry mouth	3	2.8	1	1.0
Parkinsonism[c]	3	2.8	1	1.0

[a] The table lists adverse events for which the incidence was ≥2% in the lurasidone group and was higher in the lurasidone group than the placebo group.
[b] Somnolence includes hypersomnia, sedation, somnolence, and hypersomnolence.
[c] Parkinsonism includes cogwheel rigidity, drooling, parkinsonism, psychomotor retardation, and tremor.

TABLE 4. Safety and Tolerability Parameters: Change From Baseline in Weight and Laboratory Parameters at Week 6 (Safety Population)[a]

Measure	Lurasidone			Placebo		
	N	Baseline mean	Mean change	N	Baseline mean	Mean change
Weight (kg)	105	75.8	+0.7	99	75.9	+0.4
BMI	105	26.7	+0.2	99	26.9	+0.1
	N	Baseline mean	Median change	N	Baseline mean	Median change
Total cholesterol (mg/dL)	106	201.7	+0.5	99	216.3	−1.0
Triglycerides (mg/dL)	105	137.3	−4.0	99	133.3	+2.0
Glucose (mg/dL)	105	96.2	−1.0	99	97.1	+1.0
HbA$_{1c}$ (%)	106	5.3	0.0	99	5.2	0.0
Prolactin (ng/mL)	104	14.0	+1.7	98	12.0	−0.1
Males	35	10.1	−0.1	27	6.0	+0.3
Females	69	16.0	+2.5	71	14.3	−0.3

[a] Last-observation-carried-forward endpoint. Both confirmed and nonconfirmed fasting values are reported for metabolic parameters. HbA$_{1c}$=glycosylated hemoglobin.

similar for the two groups (+0.18 cm compared with +0.05 cm; last-observation-carried-forward endpoint). There were no clinically meaningful between-group differences in laboratory measures of lipids, glycemic indices, prolactin levels, or ECG parameters (Table 4).

Based on the Columbia–Suicide Severity Rating Scale, the proportions of patients with treatment-emergent suicidal ideation or behavior in the lurasidone and placebo groups (5.5% and 7.0%, respectively) were similar, as were the proportions with treatment-emergent mania (2.8% and 5.0%, respectively).

The mean score on the Changes in Sexual Functioning Questionnaire at baseline was 35.4 for the lurasidone group and 34.1 for the placebo group. Patients in the lurasidone group were found to have significant improvement in sexual functioning at endpoint compared with those in the placebo group according to Changes in Sexual Functioning Questionnaire score (+5.1 compared with +3.1; p<0.05).

For lurasidone treatment, the likelihood of being helped or harmed was >1 (indicating that benefit from treatment [MADRS response] was more likely than harm) for nausea (likelihood of being helped or harmed, 8), somnolence (likelihood of being helped or harmed, 8), and increase of ≥7% in body weight (likelihood of being helped or harmed, 38).

DISCUSSION

This is, to our knowledge, the first placebo-controlled clinical trial that included patients with major depressive disorder associated with subthreshold hypomanic symptoms (mixed features). Lurasidone significantly improved depressive symptoms compared with placebo, based on both the primary MADRS assessment and the CGI-S assessment of overall illness severity. Significantly greater improvement in favor of lurasidone compared with placebo was ob-served from weeks 1 through 6 on the MADRS, and from weeks 2 through 6 on the CGI-S, with effect sizes in the moderate to large range for both measures at endpoint. Manic symptoms were also significantly improved in the lurasidone group, suggesting efficacy across the range of core mood symptoms associated with this disorder. In addition, treatment with lurasidone was associated with significant improvement both in anxiety symptoms and in patient-reported functional impairment.

The mixed-features variant is a severe form of major depression characterized by the presence of several manic symptoms below the threshold for hypomania in patients with no history of mania or hypomania. Since patients with

study, and no treatment-related serious adverse events. The proportion of patients who discontinued because of treatment-emergent adverse events was 2.8% in the lurasidone group and 5.0% in the placebo group (see Figure S1 in the online data supplement).

The incidence of extrapyramidal symptom-related adverse events was 2.8% in the lurasidone group and 1.0% in the placebo group. There were minimal changes in scores on the movement disorder assessments. Only 1.8% of the lurasidone group received anticholinergic medication, and none in the placebo group. The proportion of patients treated with anxiolytics was 9.2% for the lurasidone group and 12.0% for the placebo group; the proportion treated with sedatives and hypnotics was 10.1% for the lurasidone group and 11.0% for the placebo group.

Week 6 change in weight and BMI was minimal for both treatment groups (Table 4). The proportion of patients with an increase ≥7% in body weight at week 6 was 1.9% in the lurasidone group and 1.0% in the placebo group (number needed to harm=112). Mean week 6 change in waist circumference was

this condition have not been systematically studied in controlled trials, little evidence exists to guide treatment selection. This placebo-controlled study provides the first rigorous evidence that an atypical antipsychotic agent, lurasidone, may be an effective and safe treatment for this condition.

The diagnostic classification of major depression with mixed features has been a subject of much debate (36). Shared clinical characteristics, as well as similarity to bipolar patients in age at onset, family history, and course of illness (2, 8, 12, 36), suggest that patients with mixed features represent an intermediate phenotype between major depressive disorder and bipolar depression. Mixed features associated with a major depressive episode increase the risk for the development of bipolar disorder, and the presence of subthreshold manic symptoms appears to reduce treatment responsiveness to standard antidepressants, further substantiating this impression (8, 36).

We defined mixed features in this study as the presence of two or three protocol-specified manic symptoms for at least 2 weeks prior to screening. The permissible number of manic symptoms was limited to three to reduce the likelihood that patients with undiagnosed bipolar disorder would be enrolled in the study. The finding that treatment effect size was somewhat smaller in patients with three manic symptoms at baseline is consistent with previous reports that patients with admixtures of mood symptoms of opposite polarity (e.g., mixed mania) may show reduced treatment responsiveness compared with those with nonmixed forms of depression or mania (35, 36). However, further research is needed to confirm this exploratory finding in this patient population.

The presence of subthreshold hypomanic features has been shown to contribute to the heterogeneity of major depressive disorder and may add to the difficulty of achieving diagnostic reliability (8). Increased clinical efforts are needed to identify the presence of mixed features in depressed patients, both to improve case ascertainment and because the presence of as few as one or two manic symptoms has been associated with an increased risk for episode recurrence, suicide attempt, substance abuse, and poor antidepressant response (2, 8, 11, 12, 14).

The findings reported here confirm that this patient population can be identified in outpatient and community settings and provide further validation of the DSM-5 mixed features specifier in terms of its potential to better characterize symptoms associated with major depressive episodes, as well as to predict treatment response. The manic symptoms most commonly reported at study entry (racing thoughts and pressured speech) are consistent with reports in previous clinical populations (15, 17, 37). Therefore, the presence of these manic symptoms during a major depressive episode should be regarded as suggestive of the mixed-features diagnosis, and inquiry should be made to assess the presence of additional symptoms. This study also confirms previous findings that irritability, distractibility, and psychomotor agitation (nonspecific symptoms that may be

due to depression or mania) occur at relatively high rates in patients with mixed forms of major depression (38).

Lurasidone previously demonstrated efficacy in bipolar depression (25, 26), and the positive results of the present study now extend those findings to the treatment of a related disorder, major depressive disorder presenting with mixed features. The lurasidone dosage range utilized in this study (20–60 mg/day) partly overlapped with the range demonstrated to be effective for bipolar depression (20–120 mg/day). A dose-response relationship was not observed for lurasidone in a previous bipolar depression monotherapy study that evaluated lower and higher dosage ranges (25). Whether higher lurasidone dosages might provide additional efficacy in patients with mixed forms of major depression is not known.

The relatively low dosages of lurasidone utilized in this study suggest that the pharmacology of lurasidone in major depression with mixed features involves the serotonin and dopamine neuroreceptors to which lurasidone binds with high affinity (5-HT_{2A}, 5-HT_7, and D_2 receptors) (22). Given the current preclinical understanding of the role of the 5-HT_7 receptor in mediating antidepressant effects (23, 24), antagonist effects at this receptor may account for much of the observed treatment effect.

Use of lower dosages of lurasidone may have contributed to its tolerability in this study. The majority of adverse events associated with lurasidone treatment were reported as mild or moderate in severity (97.2%), and we observed low rates of study discontinuation for adverse events (2.8%) or for any reason (6.4%). Notably, rates of treatment-emergent mania and of suicidal ideation or behavior were comparable for lurasidone and placebo.

The number needed to treat to achieve a MADRS-defined response with lurasidone was 3. The number needed to harm for the two most frequently reported adverse events (nausea and somnolence) was 8, and for an increase ≥7% in body weight, it was 38. Thus, the likelihood of being helped or harmed (the ratio of number needed to harm to number needed to treat) was consistently >1, indicating that benefit from treatment with lurasidone was more likely than harm, when contrasting treatment response and specific adverse events. These results support the benefit-risk profile of lurasidone in the population studied, and they are consistent with similar findings in patients with bipolar depression (35, 39).

This study has several limitations. First, patients were eligible for study entry with either two or three manic symptoms, while DSM-5 requires at least three manic symptoms to meet criteria for the mixed features specifier. DSM-5 criteria also require manic or hypomanic symptoms to be present nearly every day during the majority of days of a major depressive episode, while in this study they were required to have occurred on most days for at least 2 weeks prior to screening. We also note that while the long-term safety of lurasidone has been established in a variety of patient populations, longer-term efficacy and safety have not been specifically studied in this patient population.

In summary, there is a pressing need for evidence-based treatments of major depressive disorder presenting with subthreshold hypomanic symptoms (mixed features), especially given its complex course and associated morbidity. Lurasidone was found to be an efficacious treatment in this patient population, with improvements observed in depressive and subthreshold hypomanic symptoms, anxiety symptoms, and functional impairment. Treatment with lurasidone was well tolerated, with a favorable benefit-risk profile in this difficult-to-treat clinical population. Further investigation is needed to determine whether these findings are applicable to other agents in the atypical antipsychotic class.

REFERENCES

1. Judd LL, Akiskal HS: The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 2003; 73:123–131
2. Angst J, Cui L, Swendsen J, et al: Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey Replication. Am J Psychiatry 2010; 167:1194–1201
3. Hoertel N, Le Strat Y, Angst J, et al: Subthreshold bipolar disorder in a US national representative sample: prevalence, correlates, and perspectives for psychiatric nosography. J Affect Disord 2013; 146: 338–347
4. Angst J, Azorin JM, Bowden CL, et al: Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. Arch Gen Psychiatry 2011; 68:791–798
5. Angst J, Gamma A, Bowden CL, et al: Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. Eur Arch Psychiatry Clin Neurosci 2013; 263:663–673
6. Benazzi F: Frequency of bipolar spectrum in 111 private practice depression outpatients. Eur Arch Psychiatry Clin Neurosci 2003; 253:203–208
7. Benazzi F, Akiskal HS: Psychometric delineation of the most discriminant symptoms of depressive mixed states. Psychiatry Res 2006; 141:81–88
8. Zimmermann P, Brückl T, Nocon A, et al: Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. Arch Gen Psychiatry 2009; 66:1341–1352
9. Perlis RH, Uher R, Ostacher M, et al: Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. Arch Gen Psychiatry 2011; 68:351–360
10. Perugi G, Angst J, Azorin JM, et al: Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. J Clin Psychiatry 2015; 76:e351–e358
11. McIntyre RS, Soczynska JK, Cha DS, et al: The prevalence and illness characteristics of DSM-5-defined "mixed feature specifier" in adults with major depressive disorder and bipolar disorder: results from the International Mood Disorders Collaborative Project. J Affect Disord 2014; 172C:259–264
12. Nusslock R, Frank E: Subthreshold bipolarity: diagnostic issues and challenges. Bipolar Disord 2011; 13:587–603
13. Akiskal HS, Benazzi F: Psychopathologic correlates of suicidal ideation in major depressive outpatients: is it all due to unrecognized (bipolar) depressive mixed states? Psychopathology 2005; 38:273–280
14. Smith DJ, Forty L, Russell E, et al: Sub-threshold manic symptoms in recurrent major depressive disorder are a marker for poor outcome. Acta Psychiatr Scand 2009; 119:325–329
15. Benazzi F: Unipolar depression with racing thoughts: a bipolar spectrum disorder? Psychiatry Clin Neurosci 2005; 59:570–575
16. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al: The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry 2013; 170:1249–1262
17. Sani G, Napoletano F, Vöhringer PA, et al: Mixed depression: clinical features and predictors of its onset associated with antidepressant use. Psychother Psychosom 2014; 83:213–221
18. Dudek D, Rybakowski JK, Siwek M, et al: Risk factors of treatment resistance in major depression: association with bipolarity. J Affect Disord 2010; 126:268–271
19. O'Donovan C, Garnham JS, Hajek T, et al: Antidepressant monotherapy in pre-bipolar depression; predictive value and inherent risk. J Affect Disord 2008; 107:293–298
20. Vieta E, Valentí M: Pharmacological management of bipolar depression: acute treatment, maintenance, and prophylaxis. CNS Drugs 2013; 27:515–529
21. Faedda GL, Marangoni C, Reginaldi D: Depressive mixed states: A reappraisal of Koukopoulos' criteria. J Affect Disord 2015; 176:18–23
22. Ishibashi T, Horisawa T, Tokuda K, et al: Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. J Pharmacol Exp Ther 2010; 334:171–181
23. Hedlund PB: The 5-HT7 receptor and disorders of the nervous system: an overview. Psychopharmacology (Berl) 2009; 206:345–354
24. Cates LN, Roberts AJ, Huitron-Resendiz S, et al: Effects of lurasidone in behavioral models of depression: role of the 5-HT7 receptor subtype. Neuropharmacology 2013; 70:211–217

25. Loebel A, Cucchiaro J, Silva R, et al: Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry 2014; 171:160–168

26. Loebel A, Cucchiaro J, Silva R, et al: Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry 2014; 171:169–177

27. First MB, Williams J, Spitzer RL, et al: Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trials Version (SCID-CT). New York, Biometrics Research, New York State Psychiatric Institute, 2007

28. Montgomery SA, Åsberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382–389

29. Guy W: ECDEU Assessment Manual for Psychopharmacology. Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976, pp 218–222

30. Young RC, Biggs JT, Ziegler VE, et al: A rating scale for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978; 133:429–435

31. Hamilton M: The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55

32. Sheehan DV: The Anxiety Disease. New York, Bantam Books, 1983

33. Posner K, Brown GK, Stanley B, et al: The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011; 168:1266–1277

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

35. Citrome L, Ketter TA, Cucchiaro J, et al: Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed. J Affect Disord 2014; 155:20–27

36. Vieta E, Valentí M: Mixed states in DSM-5: implications for clinical care, education, and research. J Affect Disord 2013; 148:28–36

37. Fiedorowicz JG, Endicott J, Leon AC, et al: Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. Am J Psychiatry 2011; 168:40–48

38. Koukopoulos A, Sani G: DSM-5 criteria for depression with mixed features: a farewell to mixed depression. Acta Psychiatr Scand 2014; 129:4–16

39. Gao K, Yuan C, Wu R, et al: Important clinical features of atypical antipsychotics in acute bipolar depression that inform routine clinical care: a review of pivotal studies with number needed to treat. Neurosci Bull 2015; 31:572–588