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ORIGINAL RESEARCH

Lurasidone for major depressive disorder with mixed features and anxiety: a post-hoc analysis of a randomized, placebo-controlled study

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Objective. The aim of this post-hoc analysis was to evaluate the efficacy of lurasidone in treating patients with major depressive disorder (MDD) with mixed features who present with mild and moderate-to-severe levels of anxiety.

Methods. The data in this analysis were derived from a study of patients meeting the DSM-IV-TR criteria for unipolar MDD, with a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥26, presenting with two or three protocol-defined manic symptoms, who were randomized to 6 weeks of double-blind treatment with either lurasidone 20–60 mg/day ($n = 109$) or placebo ($n = 100$). Anxiety severity was evaluated using the Hamilton Anxiety Rating Scale (HAM-A). To evaluate the effect of baseline anxiety on response to lurasidone, the following two anxiety groups were defined: mild anxiety (HAM-A ≤ 14) and moderate-to-severe anxiety (HAM-A ≥ 15). Change from baseline in MADRS total score was analyzed for each group using a mixed model for repeated measures.

Results. Treatment with lurasidone was associated with a significant week 6 change versus placebo in MADRS total score for patients with both mild anxiety (-18.4 vs. -12.8, $p < 0.01$, effect size [*ES*] = 0.59) and moderate-to-severe anxiety (-22.0 vs. -13.0, $p < 0.001$, *ES* = 0.95). Treatment with lurasidone was associated with a significant week 6 change versus placebo in HAM-A total score for patients with both mild anxiety (-7.6 vs. -4.0, $p < 0.01$, *ES* = 0.62), and moderate-to-severe anxiety (-11.4 vs. -6.1, $p < 0.0001$, *ES* = 0.91).

Conclusions. In this post-hoc analysis of an MDD with mixed features and anxiety population, treatment with lurasidone was associated with significant improvement in both depressive and anxiety symptoms in subgroups with mild and moderate-to-severe levels of anxiety at baseline.

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Key words: Major depressive disorder, mixed features, atypical antipsychotic, lurasidone, anxiety.

Introduction

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) incorporated a new mixed-features specifier in order to permit clinicians to note the presence of subthreshold hypomania in patients presenting with a major depressive episode.[1] The available evidence, largely from clinical study populations, suggests that major depressive disorder (MDD) with mixed features may occur in at least 25% of patients with major depression.[2–12]

In patients with a diagnosis of MDD, the estimated lifetime prevalence of an anxiety disorder is greater than 35%.[13,14] The presence of comorbid anxiety in MDD has been found to be associated with greater illness severity, chronicity, and functional impairment.[15–18]

Preliminary research suggests that patients with a diagnosis of MDD with mixed features (subthreshold hypomania) may have rates of anxiety comorbidity in the range of 45–65%.[3,11] MDD with mixed features is also

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associated with higher severity of concurrent anxiety symptoms.[10–12]

High levels of anxiety have frequently been reported to reduce the likelihood of achieving an adequate antidepressant response in patients with both unipolar MDD[19–27] and bipolar depression.[28–30] To our knowledge, no controlled trial to date has evaluated the potential impact of concurrent anxiety symptoms on response to treatment in patients presenting with MDD with mixed features.

Lurasidone is an atypical antipsychotic agent with a high affinity for dopamine D_2 ($K_i = 1.7$ nM) and for the serotonin 5-HT_{1A}, ($K_i = 6.7$ nM), 5-HT_{2A} ($K_i = 2.0$ nM), and 5-HT_7 receptors ($K_i = 0.5$ nM).[31] Lurasidone has demonstrated efficacy in the treatment of major depressive disorder with mixed features.[32] Treatment with lurasidone was associated with significant improvement in anxiety symptoms compared with placebo in patients with bipolar depression.[33–35] The purpose of the present post-hoc analysis was to assess the efficacy of lurasidone in treating MDD patients with mixed features who present with moderate-to-severe levels of anxiety.

Methods

The data utilized in this post-hoc analysis were based on a study designed to evaluate the efficacy of lurasidone for the treatment of patients with major depressive disorder presenting with subthreshold hypomanic symptoms (mixed features). Briefly, 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/day. The details of both the design and results of the study are summarized elsewhere.[32]

The diagnosis of major depressive disorder was confirmed with the Structured Clinical Interview for DSM-IV Disorders-Clinical Trial version (SCID-CT), modified to record the presence of mixed symptoms.[36] Patients were required to have a score ≥26 on the Montgomery-Åsberg Depression Rating Scale (MADRS)[37] at both the 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 the DSM-5, these nonspecific symptoms were not included in the list of eligible manic symptoms required for study entry.

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.

Efficacy assessments

The primary efficacy endpoint in the study was mean change from baseline to week 6 in MADRS total score. The key secondary efficacy endpoint was mean change from baseline to week 6 in Clinical Global Impression–Severity score (CGI-S), which rates overall illness severity on a 7-point scale.[38] Treatment effect on anxiety was evaluated based on mean change from baseline to week 6 in HAM-A total score.[39] The HAM-A scale consists of 14 items that evaluate psychic and somatic symptoms of anxiety on a 5-point severity scale, ranging from 0 (not present) to 4 (severe), with a total score range of 0 to 56. The psychic anxiety factor consists of items 1–6, and item 14 on the HAM-A scale; the somatic anxiety factor consists of items 7–13 on the HAM-A scale.

Additional secondary efficacy assessments consisted of the Young Mania Rating Scale (YMRS)[40] total score and the Sheehan Disability Scale (SDS) total score, which rates the severity of impairment in the following three functional domains: work/study, family, and social.[41] For patients who had not worked/studied during the week prior to the assessment visit, SDS total score was recorded as "missing," as long as the reason for not working/studying was not related to the disorder being treated.

Anxiety severity groups

Patients with baseline HAM-A scores ≥15 were categorized as being in the moderate-to-severe anxiety category; and baseline HAM-A scores ≤14 were categorized as mild anxiety. A score of 14 on the HAM-A has previously been identified as the optimal cutoff for defining moderate or greater levels of anxiety.[42] A separate analysis was not performed for patients with severe anxiety (baseline HAM-A total score ≥ 24) because the sample size (30/208, 14.4%) was small, and analysis results would therefore be unreliable.

Statistical analysis

Change from baseline in MADRS, CGI-S, and YMRS for lurasidone versus placebo were analyzed for the two baseline anxiety groups (mild and moderate-to-severe) using a mixed model for repeated measures (MMRM), including fixed effects for treatment, visit, anxiety subgroup, and pooled center; baseline score as a

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covariate; and treatment-by-visit, treatment-by-subgroup, subgroup-by-visit, treatment-by-subgroup-by-visit interaction terms. An unstructured covariance matrix was used for within-patient correlation. Endpoint changes in HAM–A and SDS total scores were evaluated based on an analysis of covariance (ANCOVA) of the last observation carried forward (LOCF) data. The ANCOVA model included pooled center, treatment, anxiety subgroup, and treatment-by-subgroup interaction as fixed factors, and each baseline score as a covariate. Since the current analyses were post hoc, and thus exploratory in nature, correction for multiplicity was not made. Effect sizes (Cohen's *d*)[43] were calculated as the least-squares mean difference in the change score divided by the pooled standard deviation. Treatment response was defined as a ≥50% reduction from baseline to week 6 in MADRS total score. Remission was defined as a week 6 MADRS total score ≤12. The number needed to treat to achieve response or remission was calculated as the reciprocal of the differences in responder or remitter rates in the lurasidone and placebo groups.[44]

A mediation analysis was performed, using the methodology of Baron and Kenny,[45] to evaluate the extent to which the antidepressant effect of lurasidone in this MDD/mixed population was mediated by improvement in anxiety severity (the mediating variable). Standardized parameter estimates (β values) with corresponding *p* values were calculated. The total effect of the relationship between treatment and change in MADRS total score was estimated, and the effect of lurasidone treatment on change in MADRS total score, after controlling for change in HAM–A total score, was estimated. The indirect effect was calculated as the product of the relationship between lurasidone treatment and change in HAM–A (β_2), and the relationship between change in HAM–A and change in MADRS (β_3). The proportion of the effect that is mediated was calculated as $[\beta_2 \times \beta_3]/\beta_1$. The strength of parameter estimates was interpreted using Kenny's recommendations for estimates of small (0.02), medium (0.15), and large (0.40) effect sizes.[46] Overall fit of the mediation model was assessed using various global fit indices, including the chi-square test of overall model fit; root-mean-square error of approximation (RMSEA) < 0.06;[47] and the Tucker–Lewis Index (TLI) and the Comparative Fit Index (CFI) > 0.90.[48]

Results

For the overall treatment sample, the mean (*SD*) MADRS total score was 33.3 (4.2), and the HAM–A total score was 16.9 (6.4). Baseline characteristics were approximately similar for patients with mild versus moderate-to-severe anxiety, except for a somewhat higher proportion of males in patients with mild anxiety (35.6 vs. 26.3%; Table 1).

TABLE 1. Baseline demographic and clinical characteristics

Characteristic	Mild anxiety (HAM–A ≤ 14; *n* = 90)	Moderate to severe anxiety (HAM–A ≥ 15; *n* = 118)
Male, *n* (%)	32 (35.6)	31 (26.3)
Age, years, mean (*SD*)	46.2 (12.3)	44.1 (11.8)
Race, white, *n* (%)	73 (81.1)	106 (89.8)
Current number of mixed features, n (%)		
Two features	53 (58.9)	77 (65.3)
Three features	37 (41.1)	41 (34.7)
Lifetime number of major depressive episodes, mean (*SD*)	4.0 (3.0)	4.4 (4.1)
Lifetime number of psychiatric hospitalizations, mean (*SD*)	1.2 (1.7)	1.5 (2.5)
Duration of current major depressive episode, months, mean (*SD*)	3.3 (2.5)	3.6 (2.9)
Baseline scores, mean (*SD*)		
MADRS	31.9 (3.8)	34.3 (4.1)
CGI–S	4.4 (0.6)	4.7 (0.6)
HAM–A	11.6 (2.1)	20.9 (5.5)
YMRS	10.4 (4.5)	10.9 (4.5)
SDS	19.8 (4.5)	20.6 (5.5)

CGI–S = Clinical Global Impression–Severity scale; HAM–A = Hamilton Rating Scale for Anxiety; MADRS = Montgomery–Åsberg Depression Rating Scale; SDS = Sheehan Disability Scale; YMRS = Young Mania Rating Scale.

Mean HAM–A total score in patients with mild and moderate-to-severe anxiety was 11.6 and 20.9, respectively. At baseline, MADRS and HAM–A scores were moderately correlated ($r = 0.39$), while YMRS and HAM–A total scores were minimally correlated ($r = 0.17$).

The mean daily doses of lurasidone in patients with mild and moderate-to-severe anxiety were 37.8 and 35.1 mg, respectively. The completion rates in the lurasidone and placebo groups were 93.6 versus 80.0%, respectively, in patients with mild anxiety, and 93.5 versus 89.5%, respectively, in patients with moderate-to-severe anxiety.

Efficacy

MADRS

Treatment with lurasidone was associated with significantly greater week 6 improvement compared with placebo on MADRS total score in patients with both mild and moderate-to-severe levels of anxiety, with effect sizes of 0.59 and 0.95, respectively (Table 2). In both anxiety subgroups, significantly greater improvement in the MADRS was observed for lurasidone compared with placebo starting at week 3 (Figure 1). For the full-intent-to-treat population, the HAM–A total score and the interaction of treatment by HAM–A total score were not significant as covariates in the MMRM model ($p = 0.27$ and 0.11, respectively). Responder rates were significantly higher for lurasidone versus placebo in patients with both

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TABLE 2. Least-squares mean change at week 6 in efficacy measures by baseline anxiety severity for lurasidone versus placebo in patients with mild and moderate-to-severe anxiety

	n	DB baseline, mean (*SD*)	Mean (*SE*) change	*p* value	Effect size
MADRS total					
Moderate-to-severe anxiety					
Lurasidone	61	34.2 (4.4)	–22.0 (1.3)	<0.0001	0.95
Placebo	57	34.5 (3.9)	–13.0 (1.3)		
Mild anxiety					
Lurasidone	47	32.0 (4.0)	–18.5 (1.4)	<0.01	0.60
Placebo	43	31.8 (3.7)	–12.9 (1.6)		
CGI–Severity					
Moderate-to-severe anxiety					
Lurasidone	61	4.7 (0.6)	–2.0 (0.1)	<0.0001	0.84
Placebo	57	4.6 (0.6)	–1.1 (0.2)		
Mild anxiety					
Lurasidone	47	4.3 (0.6)	–1.6 (0.2)	n.s.	0.31
Placebo	43	4.5 (0.6)	–1.3 (0.2)		
HAM–A total[a]					
Moderate-to-severe anxiety					
Lurasidone	60	21.2 (5.8)	–11.4 (0.9)	<0.0001	0.91
Placebo	56	20.5 (5.1)	–6.1 (0.9)		
Mild anxiety					
Lurasidone	45	11.5 (2.1)	–8.2 (1.0)	<0.01	0.63
Placebo	42	11.6 (2.2)	–4.6 (1.1)		
YMRS total					
Moderate-to-severe anxiety					
Lurasidone	61	11.6 (4.7)	–7.5 (0.5)	<0.0001	0.86
Placebo	57	10.2 (4.3)	–4.6 (0.5)		
Mild anxiety					
Lurasidone	47	10.4 (4.3)	–6.4 (0.5)	n.s.	0.28
Placebo	43	10.4 (4.7)	–5.4 (0.6)		
SDS total[a]					
Moderate-to-severe anxiety					
Lurasidone	36	20.3 (5.5)	–12.4 (1.3)	<0.001	0.80
Placebo	39	21.0 (5.3)	–6.6 (1.3)		
Mild anxiety					
Lurasidone	34	19.4 (4.3)	–9.9 (1.3)	0.04	0.52
Placebo	30	19.9 (4.8)	–6.1 (1.4)		

Mild anxiety = HAM–A total score ≤ 14; moderate-to-severe anxiety = HAM–A total score ≥ 15. CGI–S = Clinical Global Impression–Severity scale; HAM–A = Hamilton Rating Scale for Anxiety; MADRS = Montgomery–Åsberg Depression Rating Scale; SDS = Sheehan Disability Scale; YMRS = Young Mania Rating Scale; n.s. = not significant.

[a] ANCOVA analysis; SDS analysis was limited to individuals who were employed.

mild and moderate-to-severe levels of baseline anxiety, with number needed to treat (*NNT*) values of 4 and 3, respectively; remission rates were nonsignificantly higher in patients with mild anxiety, and significantly higher in patients with moderate-to-severe anxiety, with *NNT* values of 6 and 4, respectively (Figure 2).

CGI–S

Treatment with lurasidone was associated with significantly greater week 6 improvement compared with placebo on CGI-Severity score in patients with moderate-to-severe levels of anxiety (Cohen's $d = 0.84$), but not in those with mild anxiety (Cohen's $d = 0.31$; Table 2).

HAM–A

For all patients, baseline to week 6 improvement in HAM-A total score was significantly greater for lurasidone compared with placebo (-9.9 vs. -5.4, $p < 0.001$, Cohen's $d = 0.78$), with significant week 6 improvement in favor of lurasidone observed for 6 of 7 items on both the HAM-A psychic and somatic anxiety factors (Figure 3).

Treatment with lurasidone was associated with significantly greater week 6 improvement compared with placebo on HAM-A total score in patients with both mild and moderate-to-severe levels of anxiety, with effect sizes of 0.63 and 0.91, respectively (Table 2). On the HAM-A psychic anxiety factor score, week 6 improvement was

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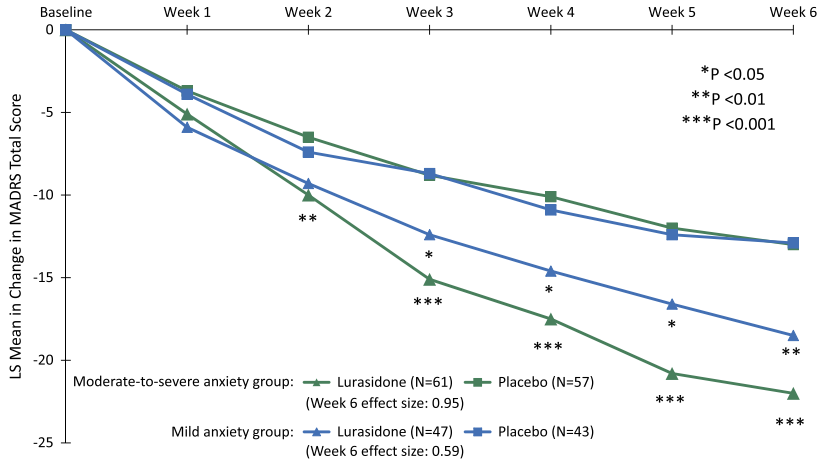
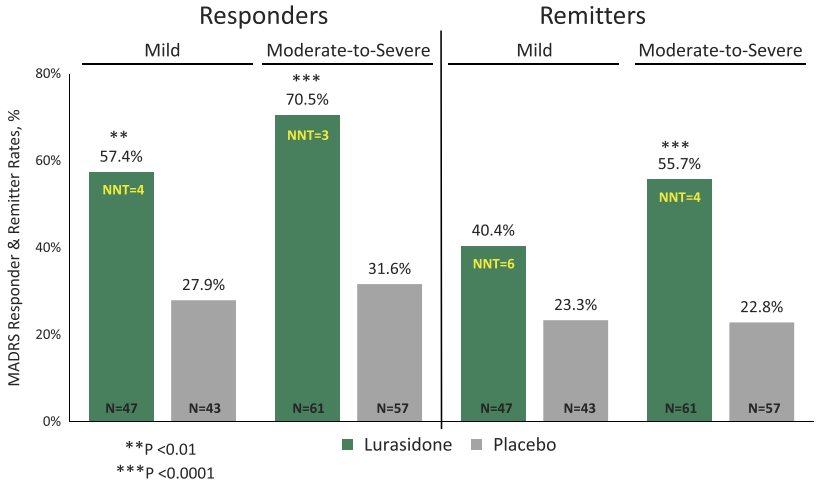


FIGURE 1. Least squares mean change from baseline in MADRS total score for lurasidone versus placebo in patients with mild and moderate-to-severe anxiety.



Responder criteria: ≥50% reduction from baseline-to-week 6 in MADRS total score;
Remission criteria: week 6 MADRS total score ≤12; Logistic regression (unadjusted) at LOCF-endpoint

FIGURE 2. MADRS responder and remission rates for lurasidone versus placebo in patients with mild and moderate-to-severe anxiety (LOCF endpoint analysis).

greater for lurasidone versus placebo in patients with both mild (-6.7 vs. -4.7, $p < 0.05$, Cohen's $d = 0.5$) and moderate-to-severe (-8.3 vs. -4.4, $p < 0.0001$, Cohen's $d = 1.0$) levels of anxiety. On the HAM-A somatic anxiety factor score, week 6 improvement was greater for lurasidone versus placebo in patients with both mild (-2.2 vs. -0.6, $p < 0.01$, Cohen's $d = 0.7$) and moderate-to-severe (-2.5 vs. -1.2, $p < 0.01$, Cohen's $d = 0.5$) levels of anxiety.

Mediation analysis

Figure 4 summarizes the result of the mediation model, which found a moderate effect for the relationship between treatment with lurasidone and improvement in HAM-A total score ($\beta_2 = -0.29$, $p < 0.0001$), and a large effect for the relationship between improvement in HAM-A total score and improvement in MADRS total score ($\beta_3 = 0.73$, $p < 0.0001$). The direct effect of lurasidone on improvement in MADRS total score, after controlling for the effect of the mediator variable (change in HAM-A), was significant but moderate in size ($\beta = -0.14$, $p < 0.01$). These results are consistent with a substantial degree of mediation, with indirect effects of lurasidone on improvement in MADRS total score accounting for 60.5% of the total effect and direct effects accounting for 39.5% of the total effect.

YMRS

Treatment with lurasidone was associated with significantly greater week 6 improvement on YMRS total score compared with placebo in patients with moderate-to-severe levels of anxiety (Cohen's $d = 0.63$), but not mild anxiety (Cohen's $d = 0.28$; Table 2). The proportions of patients reporting the presence of irritability (YMRS item 5 score ≥ 2) were 50.0 and 61.9% for patients with mild (HAM-A ≤14) and moderate-to-severe (HAM-A

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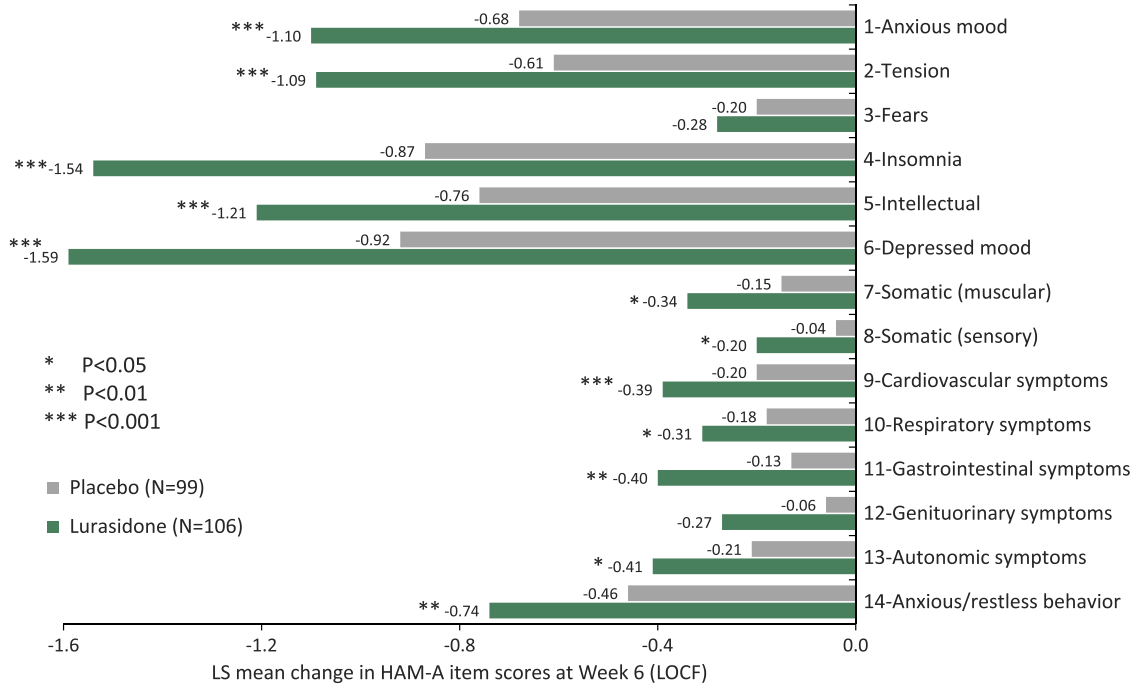

FIGURE 3. Mean baseline to week 6 change in HAM–A item scores (LOCF endpoint analysis).

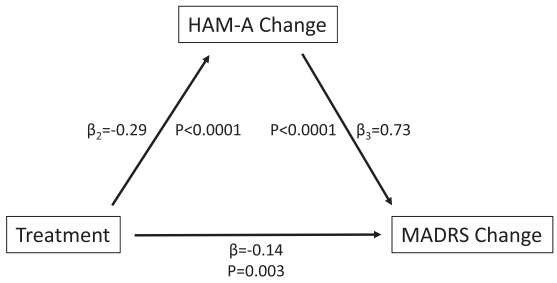

FIGURE 4. Mediation model of the effect of HAM–A change on antidepressant response to lurasidone.

≥15) baseline levels of anxiety, respectively. Similarly, the proportions of patients reporting the presence of psychomotor agitation (YMRS item 2 score ≥ 2) were 31.1 and 39.8% for patients with mild and moderate-to-severe baseline levels of anxiety, respectively.

SDS

Treatment with lurasidone was associated with significantly greater week 6 improvement compared with placebo on SDS total score in patients with both mild and moderate-to-severe levels of anxiety, with effect sizes of 0.52 and 0.80, respectively (Table 2).

Tolerability

Overall, the percentage of patients with one or more treatment-emergent adverse events was similar for lurasidone versus placebo in the mild anxiety group (38.3 vs. 39.5%) and in the moderate-to-severe anxiety group (41.9 vs. 36.8%). The rates of study discontinuation due to an adverse event in the lurasidone and placebo groups were 2.1 vs. 6.7%, respectively, in patients with mild anxiety, and 3.2 versus 3.5%, respectively, in patients with moderate-to-severe anxiety. In patients with mild anxiety, nausea was the only treatment-emergent adverse event that occurred with a frequency ≥5%, and more frequently on lurasidone versus placebo (10.6 vs. 4.7%, number needed to harm [*NNH*] = 17). In patients with moderate-to-severe anxiety, two events occurred more frequently on lurasidone versus placebo, somnolence and akathisia (6.5 vs. 1.8% for both events; NNH = 22).

Discussion

Mixed features (subthreshold hypomanic symptoms) occur in approximately a third of patients with unipolar

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depression and are associated with greater illness severity, chronicity, and functional impairment compared to pure forms of MDD.[2–12] In MDD patients without mixed features, the presence of concurrent anxiety has been shown to reduce the likelihood of achieving an adequate antidepressant response.[19–27] We report here the results of a post-hoc analysis of a placebo-controlled, 6-week trial of MDD presenting with mixed features and anxiety which found that treatment with lurasidone significantly improved depressive symptoms in a subgroup of patients with moderate-to-severe anxiety at baseline. Significant improvement was also noted in the subgroup with mild anxiety at baseline. Effect sizes for lurasidone were notably larger in the moderate-to-severe (vs. mild) anxiety severity subgroup across multiple outcome measures, including MADRS total score (0.95 vs. 0.59), CGI-S (0.84 vs. 0.30), and YMRS (0.63 vs. 0.28).

In the current analysis, 56.7% of patients with MDD with mixed features presented with moderate-to-severe levels of baseline anxiety. This is comparable to rates previously reported for MDD populations not selected for mixity.[13–17] Treatment of the current MDD/mixed population with lurasidone was associated with significant improvement in HAM-A total score, with larger effect sizes in the moderate-to-severe (vs. mild) anxiety severity subgroup, and with significant efficacy in treating the psychic and somatic symptoms of anxiety in both anxiety severity subgroups.

The results of a mediation analysis found that a significant proportion (60.5%) of the antidepressant effect of lurasidone in this MDD/mixed population was mediated indirectly by improvement in anxiety symptoms. This may in part explain the larger effect sizes observed for endpoint change in MADRS scores in the moderate-to-severe anxiety subgroup.

The presence of comorbid anxiety, or high levels of anxiety symptom severity, has been reported to have a negative effect on antidepressant treatment response in both unipolar and bipolar depression.[19–30] Notably, treatment with lurasidone has previously demonstrated significant anxiolytic treatment effects in three separate 6-week trials in bipolar depression.[33–35] While further studies are necessary to confirm these findings, the results of the current analysis, taken together with the consistent improvements in HAM-A scores observed in prior bipolar depression studies, suggest that lurasidone may be a useful treatment for mixed forms of major depression associated with anxiety.

In the current MDD/mixed population, higher levels of anxiety severity at baseline were associated with increased rates of irritability (based on a YMRS item 5 score ≥ 2) and psychomotor agitation (based on a YMRS item 2 score ≥ 2). A significant association between irritability and current and/or prior anxiety has previously been reported in both unipolar[49–51] and bipolar[52] depression populations. Increased irritability has also been reported in bipolar patients with comorbid anxiety during inter-episode intervals.[53]

Neither irritability nor anxiety are part of the formal criteria for the DSM-5 diagnosis of MDD with mixed features. However, the high degree of concurrence between irritability and anxiety in the current analysis raises a question as to whether irritability and anxiety are more usefully viewed as core clinical symptoms of MDD with mixed features, or whether (as presently viewed in the DSM-5) they are too nonspecific to qualify as diagnostic criteria. A recent analysis of patients with bipolar depression with mixed features[54] found that broadening mixed features criteria by including additional, non-DSM-5 symptoms (e.g., irritability, distractibility, agitation) yielded a mixed-depression subgroup that was three times larger than the more restrictive DSM-5 definition. However, this more inclusively defined mixed-depression subgroup had many of the same clinical characteristics as the restrictive DSM-5 subgroup, including higher rates of comorbid anxiety and apparent reduced response to standard antidepressants.[55–57] The larger effect sizes observed in the moderate-to-severe anxiety subgroup in the current analysis of an MDD with mixed features population, and similarly larger effect sizes in a separate analysis of a subgroup of patients with irritability in this MDD/mixed population (see Swann *et al.* in the current issue), provide support for the hypothesis that anxiety/irritability symptoms may be clinical biomarkers of treatment responsivity, and thus are best viewed as core components of the MDD with mixed features presentation.

The receptor binding profile of lurasidone suggests a plausible anxiolytic mechanism of action for the current findings, with high affinity (as a partial agonist) for the serotonin 5-HT_{1A} receptor and (as an antagonist) at 5-HT_7 receptors, both of which have been implicated as anxiety substrates.[31,58–62] The observed reduction in anxiety associated with pharmacologic inhibition, or receptor inactivation using knockout mouse models, suggests that both the 5-HT_{1A} and 5-HT_7 receptors may mediate anxiety symptoms and behaviors.[58,62]

Previous studies have reported that the presence of prominent anxiety in MDD was associated with increased illness severity and functional impairment.[15–18] In the current analysis, there were minimal differences between patients in the moderate-to-severe and mild anxiety severity subgroups on measures of global illness severity (CGI-S) and functional impairment (SDS self-ratings) at study baseline. SDS disability ratings were in the markedly impaired range at baseline for both anxiety severity subgroups, which may reflect the high degree of severity intrinsic to the MDD/mixed features diagnosis.[2,4,12] Treatment with lurasidone was associated with significant endpoint improvement in SDS impairment

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ratings, with moderate to large effect sizes in patients with both mild and moderate-to-severe anxiety severity.

Baseline anxiety severity appeared to have minimal impact on the tolerability of lurasidone treatment. Rates of discontinuation due to an adverse event were similar for lurasidone (vs. placebo) in the moderate-to-severe anxiety subgroup (3.2 vs. 3.5%, respectively), and in the mild anxiety subgroup (2.1 vs. 6.7%, respectively). Adverse event rates were similarly low in both anxiety severity subgroups.

The current findings are limited by the post-hoc nature of the analysis, and therefore require confirmation in future studies. Patients were not specifically selected for the presence of moderate-to-severe anxiety, and it is possible that anxiety symptom severity in the current study was lower than the severity of anxiety observed in naturalistic populations of MDD patients presenting with mixed features. In addition, it is possible that anxiety severity assessments were influenced by the presence of irritability and/or agitation in some patients. Patients with a comorbid primary axis I anxiety disorder were excluded from study entry, so that the current results may not be generalizable to depressed patients with severe syndromic levels of anxiety comorbidity. HAM-A ratings were obtained at baseline and at week 6; therefore, no information is available on the temporal pattern of improvement in anxiety symptom severity over the 6-week study.

In this post-hoc analysis of an MDD with mixed features and anxiety study population, treatment with lurasidone was associated with significant improvement in both depressive and anxiety symptoms in subgroups with mild and moderate-to-severe levels of anxiety at baseline.

A mediation analysis indicated that improvement in depressive symptom severity on lurasidone was partially mediated by improvement in anxiety. Given the high rates of anxiety reported in patients with a diagnosis of MDD with mixed features, the combined antidepressant and anxiolytic efficacy of lurasidone makes it a potentially useful treatment option in this common and difficult-to-treat clinical population.

Disclosures

Drs. Tsai, Mao, Ng-Mak, Pikalov, and Loebel are employees of Sunovion Pharmaceuticals Inc. Dr. Thase reports grants and other from Sunovion Pharmaceuticals Inc. during the conduct of the study; grants and other from Alkermes; grants and other from Forest Laboratories (an Allergan affiliate); grants from the National Institute of Mental Health; grants and other from Otsuka; grants from PharmaNeuroboost; grants from Roche; other from Astra-Zeneca; other from Bristol-Myers Squibb; other from Cerecor; other from Eli Lilly; other from the Gerson Lehman Group; other from GlaxoSmithKline; other from Guidepoint Global; other from Lundbeck; other from MedAvante; other from Merck; other from Neuronetics; other from Novartis; other from Ortho-McNeil Pharmaceuticals; other from Pamlab; other from Pfizer; other from Shire; other from Takeda; other from the American Psychiatric Association; other from Guilford Publications; other from Herald House; other from W.W. Norton & Company–all outside the submitted work.

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