Notice of correction: This article's text and Tables 2 and 3 were updated on August 29, 2016, at the request of the authors.

Efficacy of Lurasidone in Adults Aged 55 Years and Older With Bipolar Depression:

Post Hoc Analysis of 2 Double-Blind, Placebo-Controlled Studies

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ABSTRACT

Objective: The aim of this post hoc analysis was to evaluate the efficacy of lurasidone in patients aged 55 years and older with bipolar depression.

Methods: A post hoc analysis was performed on the older adult subgroup (n = 142) of outpatients meeting *DSM-IV-TR* criteria for bipolar I depression in 2 placebo-controlled, 6-week, randomized, double-blind studies conducted from 2009–2012: a monotherapy study comparing fixed flexible-dose ranges of lurasidone 20–60 mg/d or 80–120 mg/d with placebo and an adjunctive therapy study comparing flexible doses of lurasidone 20–120 mg/d with placebo adjunctive to either lithium or valproate. The primary endpoint was mean change at week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

Results: In the randomized sample, the proportion of older adults was 88/505 (17.4%) in the monotherapy study and 54/348 (15.5%) in the adjunctive therapy study. In the older adult subgroup in the monotherapy study, mean change at week 6 in the MADRS was significantly greater for lurasidone versus placebo (−14.8 vs −7.1; $P = .003$; effect size, 0.83; pooled doses), and in the adjunctive therapy study, mean change for lurasidone was not significantly different from placebo (−13.9 vs −11.1; $P = .398$; effect size, 0.26). Discontinuation rates due to adverse events for lurasidone versus placebo were similar for the monotherapy (6.8% vs 6.9%) and adjunctive therapy (3.8% vs 7.1%) studies. Lurasidone had minimal effects on metabolic laboratory values.

Conclusions: The results of these post hoc analyses, which assessed the efficacy of lurasidone in older adults with bipolar disorder, found that monotherapy was significantly effective while adjunctive therapy was not associated with significant improvement. Both monotherapy and adjunctive therapy with lurasidone were safe and well-tolerated in this older adult population.

Trial Registration: ClinicalTrials.gov identifiers: NCT00868699, NCT00868452.

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Bipolar disorder typically has an early age at onset, with an estimated prevalence of 3.9% in adults aged 18–30 years.[1] Due to its chronicity, bipolar disorder persists into the fifth decade and beyond in a large proportion of patients. The prevalence in older adults is estimated to range from 0.5%–1%,[1,2] with approximately 10% having a late-onset variant of the illness that includes a first episode of mania occurring after the age of 50.[1] As the course of illness progresses, episodes of depression increasingly predominate over episodes of mania[3,4] and are associated with functional impairment[5–8] and increased direct and indirect health care costs.[4,8,9] Despite relatively low prevalence among older adults in the community, bipolar disorder is overrepresented as a proportion of geriatric outpatient medical visits, geriatric inpatient admissions (8%–10%), and geriatric emergency department presentations with psychiatric emergencies (17%).[2,10]

Currently, 3 medications are approved by the US Food and Drug Administration (FDA) for the treatment of bipolar depression: the combination of fluoxetine/olanzapine,[11–13] quetiapine,[14] and lurasidone.[15,16] To date, no randomized, placebo-controlled clinical trials have been reported that specifically evaluate the efficacy of an atypical agent for the treatment of bipolar depression in older adults. The presumption is that results from clinical trials in younger patients will generalize to the older adult population; however, this is not certain. Furthermore, older adults are more vulnerable to adverse drug effects and drug-drug interactions; thus, evaluation in this population is clinically relevant.

Lurasidone is an atypical antipsychotic with high affinity for D_2, 5-HT_{2A}, and 5-HT_7 receptors (as an antagonist); moderate affinity for 5-HT_{1A} receptors (as a partial agonist); and no appreciable affinity for H_1 and M_1 receptors.[17] Lurasidone is metabolized primarily by cytochrome P450 3A4 (CYP3A4)[18] and therefore should not be administered with potent CYP3A4 inhibitors or inducers. Moderate inhibitors may be coadministered, but the dose of lurasidone should not exceed 80 mg/d. The elimination half-life of lurasidone is 18 hours,[17,18] permitting once-per-day dosing. Results from an extensive clinical development program[19] in schizophrenia and bipolar depression indicate that lurasidone has no clinically meaningful effects on electrocardiogram (ECG) parameters and minimal effects on weight, metabolic parameters, and glycemic indices.

Because of its favorable safety profile in younger adults, lurasidone would appear to be a good candidate for the treatment of depressive episodes in older adults. This post hoc analysis evaluated the efficacy and safety of lurasidone in older adults aged 55 years and older presenting with a diagnosis of bipolar depression.

Clinical Points

- To date, no randomized trials have evaluated the efficacy of atypical antipsychotics for the treatment of bipolar depression in older adults.
- Results from this post hoc analysis suggest that monotherapy with lurasidone is an effective treatment for bipolar depression in older adults, primarily in the age range of 55–69 years. In contrast, treatment with lurasidone adjunctive with lithium or valproate was not associated with significant improvement.
- Whether administered as monotherapy or adjunctively with lithium or valproate, lurasidone was found to be well-tolerated and to have minimal effect on metabolic parameters in older adults.

METHODS

Data in this post hoc analysis derive from 2 multiregional studies[17,18] conducted in the United States and 7 other countries from 2009–2012 that evaluated the efficacy of lurasidone for the treatment of bipolar type I depression when administered as a monotherapy or as an adjunctive with lithium or valproate. Details of the design of the individual studies (NCT00868699 and NCT00868452) are summarized elsewhere. Briefly, both studies were double-blind, placebo-controlled, parallel-group trials. Following a washout period of at least 3 days, patients were randomly assigned to receive 6 weeks of treatment with lurasidone or placebo. In the 3-arm monotherapy study, patients were randomly assigned to 1 of 2 fixed flexible-dose ranges of either 20–60 mg or 80–120 mg of lurasidone daily or to placebo. In the 2-arm adjunctive therapy study, patients underwent stratified randomization based on concurrent treatment with either lithium or valproate to either adjunctive lurasidone at 20–120 mg/d or to placebo. In the monotherapy study, for patients randomized to lurasidone 20–60 mg/d, treatment was initiated at 20 mg/d for days 1–7. For patients randomized to lurasidone 80–120 mg/d, treatment was initiated at 20 mg/d for days 1–2, 40 mg/d for days 3–4, 60 mg/d for days 5–6, and 80 mg/d on day 7. In both treatment arms, lurasidone dosing adjustments within the assigned dosing range were permitted after 7 days to optimize efficacy and tolerability. In the adjunctive study, lurasidone treatment was initiated at 20 mg/d on days 1–3. It was increased to 40 mg/d on days 4–6 and to 60 mg/d on day 7. After the first week, lurasidone could be adjusted at weekly intervals in 20-mg increments or decrements within the dose range of 20–120 mg/d, based on investigator judgment.

Both studies were approved by an institutional review board at each investigational site and were conducted in accordance with the International Council for Harmonisation (formerly the International Conference on Harmonisation) Good Clinical Practices guidelines and with the ethical principles of the World Medical Association Declaration of Helsinki. Written informed consent was obtained prior to study entry. An independent data and safety monitoring board reviewed and monitored patient data in both studies.

Both studies enrolled outpatients aged 18–75 years with bipolar I disorder who were experiencing a major depressive episode (*DSM-IV-TR* criteria, ≥ 4 weeks and < 12 months in duration), with or without rapid cycling, without psychotic features, and with a history of at least 1 lifetime bipolar manic or mixed manic episode. Diagnosis was confirmed by the Mini-International Neuropsychiatric Interview[20] and the Bipolarity Index.[21] A Montgomery-Åsberg Depression Rating Scale (MADRS)[22] score of ≥ 20 and a Young Mania Rating Scale (YMRS)[23] score of ≤ 12 were required at both screening and baseline. This post hoc analysis assessed the group of patients who were 55 years and older in each study at the time of the screening visit.

Efficacy and Safety Assessments

In both studies, efficacy assessments were obtained at baseline and weekly intervals. The primary, a priori efficacy endpoint was mean change from baseline to week 6 in the MADRS total score. Secondary efficacy assessments included the mean change from baseline to week 6 in the depression severity score of the Clinical Global Impressions, Bipolar–Severity of Illness depression scale (CGI-BP-S),[24] the Quick Inventory of Depressive Symptomatology–Self Report ($QIDS\text{-}SR_{16}$),[25] Hamilton Anxiety Rating Scale (HARS),[26] Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF),[27] and Sheehan Disability Scale (SDS).[28]

Safety and tolerability were assessed by the incidence and severity of adverse events during the study. Additional safety evaluations included vital signs, laboratory tests, 12-lead ECGs, and physical examinations. Treatment-emergent mania was defined, a priori, as a YMRS total score of ≥ 16 on any 2 consecutive visits or at the final assessment, or an adverse event of mania or hypomania. Suicidal ideation and behavior were assessed using the Columbia–Suicide Severity Rating Scale (C-SSRS).[29]

Statistical Methods

The modified intent-to-treat population (mITT) consisted of randomized patients who received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment. For the total mITT population for each individual study (ie, monotherapy and adjunctive therapy), change from baseline in the MADRS (primary) and the CGI-BP-S was assessed using a mixed model for repeated measures (MMRM) analysis that included fixed effect terms for treatment, visit, pooled center, and baseline score as a covariate and a treatment-by-visit interaction term, and an unstructured covariance matrix for within-patient correlation. Changes from baseline in additional efficacy measures were evaluated using an analysis of covariance model using last observation carried forward (LOCF) with fixed effects for treatment, pooled center, and baseline score as a covariate. In the monotherapy study, a dose-by-treatment analysis did not find a significant interaction

Table 1. Baseline Characteristics (mITT population)

Characteristic	Monotherapy		Adjunctive Therapy With Lithium or Valproate	
	Lurasidone (pooled doses)[a] (n = 56)	Placebo (n = 27)	Lurasidone, 20–120 mg/d (n = 26)	Placebo (n = 27)
Female, n (%)	38 (67.9)	14 (51.9)	14 (53.8)	16 (59.3)
Age, y, mean (SD)	59.8 (4.2)	60.1 (4.5)	59.1 (3.3)	60.0 (4.6)
Duration of current episode, wk, mean (SD)	11.3 (8.5)	9.6 (5.6)	11.9 (8.2)	12.4 (9.1)
Race, n (%)				
White	50 (89.3)	23 (85.2)	22 (84.6)	22 (81.5)
Black/African-American	4 (7.1)	1 (3.7)	2 (7.7)	4 (14.8)
Other	2 (3.6)	3 (11.1)	2 (7.7)	1 (3.7)
≥ 2 Prior hospitalizations for depression, n (%)	28 (50.0)	12 (44.4)	9 (34.6)	13 (48.1)
Adjunctive treatment, n (%)				
Lithium	…	…	11 (42.3)	9 (33.3)
Valproate	…	…	15 (57.7)	18 (66.7)
MADRS score, mean (SD)	30.4 (4.7)	29.7 (4.8)	31.3 (5.4)	29.6 (5.0)
CGI-BP-S score, mean (SD)	4.6 (0.7)	4.4 (0.6)	4.6 (0.9)	4.5 (0.6)

[a]Pooled data shown for 2 fixed flexible-dosing arms (20–60 mg/d; 80–120 mg/d).
Abbreviations: CGI-BP-S = Clinical Global Impressions, Bipolar–Severity of Illness depression scale, MADRS = Montgomery-Åsberg Depression Rating Scale, mITT = modified intent-to-treat population (randomized patients [n = 136] received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment).
Symbol: … = not applicable.

effect; therefore, to provide more adequate sample sizes for post hoc analyses, the 2 fixed-flexible monotherapy dose groups (20–60 mg/d and 80–120 mg/d) were pooled. Efficacy for each individual dose group was also calculated for the MADRS and CGI-BP-S.

The criterion for treatment response was ≥ 50% reduction from baseline to LOCF-endpoint in the MADRS total score, and remission was defined as a MADRS total score ≤ 12 at LOCF-endpoint. The proportion of responders and remitters was compared between the lurasidone and placebo groups using logistic regression. The number needed to treat to attain an additional responder was derived for the lurasidone group as follows: number needed to treat = 1/(lurasidone response rate – placebo response rate). Cohen *d* effect sizes (*d*) were calculated for efficacy measures as the difference in the change scores for the treatment groups divided by the pooled standard deviation.

The safety population consisted of all randomized patients who received at least 1 dose of study medication. Descriptive statistics were used for safety variables.

RESULTS

Of the combined total of 853 patients randomized in the 2 parent studies, 142 (16.6%) were aged ≥ 55 years and were included in the current post hoc analysis. Baseline characteristics were similar in each older adult treatment group except for a lower percentage of men among patients randomized to the lurasidone group in the monotherapy study (Table 1). For the combined sample overall, the mean age of patients in the current analysis was 60 years; 11% were 65 years or older.

In the older patient subgroup in the monotherapy study, the mean modal daily dose of lurasidone was 34.6 mg for the 20–60 mg/d group and 96.0 mg for the 80–120 mg/d group. In the adjunctive therapy study, the mean modal daily dose of lurasidone was 76.2 mg.

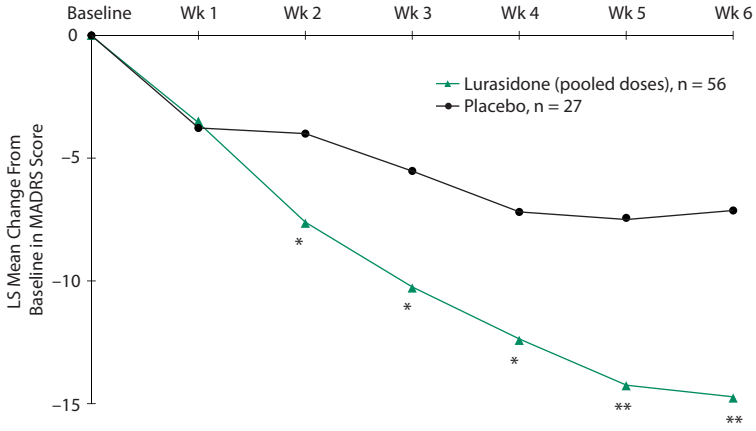
A higher proportion of older patients in the adjunctive therapy study received valproate at study entry compared to lithium (Table 1). The mean baseline dose of lithium in the lurasidone and placebo groups, respectively, was 845 mg/d and 817 mg/d; lithium concentrations were similar in the lurasidone and placebo groups, respectively, at baseline (0.76 mEq/L vs 0.84 mEq/L) and week 6 (0.96 mEq/L vs 0.73 mEq/L). The mean baseline dose of valproate in the lurasidone and placebo groups, respectively, was 1,120 mg/d and 1,169 mg/d; valproate concentrations were also similar at baseline (68.2 mg/L vs 67.4 mg/L) and at week 6 (84.9 mg/L vs 75.6 mg/L).

In the older patient subgroup in the monotherapy study, discontinuation rates (total; and due to adverse events) were similar for lurasidone 20–60 mg/d (28.6%; 7.1%), lurasidone 80–120 mg/d (22.6%; 6.5%), and placebo (27.6%; 6.9%). In the older patient subgroup in the adjunctive therapy study, total discontinuation rates were somewhat higher in the lurasidone group compared with the placebo group (19.2% vs 14.3%), but discontinuation rates due to adverse events were approximately similar (3.8% vs 7.1%).

Efficacy

Monotherapy study. In a pooled analysis of the monotherapy study, least squares (LS) mean change for lurasidone was significantly different from placebo on the MADRS from weeks 2–6 (Figure 1). Significant efficacy was also observed at week 6 in a pooled analysis of the CGI-BP-S (Table 2). On additional secondary efficacy measures, the LOCF-endpoint effect size for pooled doses of lurasidone ranged from 0.26–0.51, and was statistically significant on

Figure 1. Monotherapy With Lurasidone (pooled doses of 20–60 mg/d and 80–120 mg/d)[a] vs Placebo: LS Mean Change in MADRS Total Score for the mITT Population[b]



[a]Effect size for pooled lurasidone dose groups = 0.81.
[b]Assessed using a mixed model for repeated measures (MMRM) analysis.
*P < .05. **P < .01.
Abbreviations: LS = least squares, MADRS = Montgomery-Åsberg Depression Rating Scale, mITT = modified intent-to-treat.

Table 2. Monotherapy With Lurasidone: Endpoint Change in Primary and Secondary Efficacy Measures for the mITT Population

Scores	n	Baseline Mean (SD)	Endpoint Change LS Mean (SE)	*P* Value	Effect Size
MADRS total score (primary endpoint)[a]					
Lurasidone (pooled doses)	56	30.4 (4.7)	−14.8 (1.4)	.003	0.83
Placebo	27	29.7 (4.8)	−7.1 (2.0)		
CGI-BP-S score[a]					
Lurasidone (pooled doses)	56	4.6 (0.7)	−1.7 (0.2)	.012	0.69
Placebo	27	4.4 (0.6)	−0.8 (0.3)		
QIDS-SR_{16} total score[b]					
Lurasidone (pooled doses)	56	14.8 (3.5)	−6.1 (0.7)	.035	0.51
Placebo	27	14.4 (3.2)	−3.3 (1.1)		
HARS total score[b]					
Lurasidone (pooled doses)	52	16.1 (5.8)	−6.0 (1.0)	.069	0.44
Placebo	27	15.9 (6.5)	−2.6 (1.5)		
Q-LES-Q-SF score[b]					
Lurasidone (pooled doses)	51	35.7 (10.6)	+13.6 (2.2)	.279	0.26
Placebo	26	28.8 (10.5)	+9.0 (3.4)		
SDS total score[b]					
Lurasidone (pooled doses)	35	20.8 (4.5)	−8.9 (1.1)	.315	0.32
Placebo	16	19.8 (4.0)	−6.5 (1.9)		

[a]Mixed model for repeated measures analysis.
[b]Analysis of covariance—last observation carried forward analysis.
Abbreviations: CGI-BP-S = Clinical Global Impressions, Bipolar–Severity of Illness depression scale; HARS = Hamilton Anxiety Rating Scale; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; mITT = modified intent-to-treat population; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; QIDS-SR_{16} = Quick Inventory of Depressive Symptomatology–Self Report, 16 item; SDS = Sheehan Disability Scale.

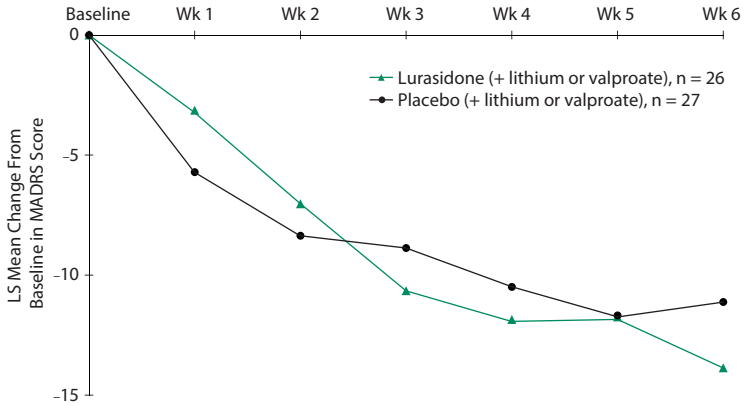
the patient-rated QIDS-SR_{16}, but it was not significant on the HARS, Q-LES-Q-SF, and SDS (Table 2).

For older adults in the monotherapy study, treatment with lurasidone was associated with significantly greater week 6 improvement for each fixed-flexible daily dose range (20–60 mg/d and 80–120 mg/d) on the MADRS score (−15.4, P < .01) and (−14.1, P < .05) vs placebo (−7.1), respectively, and on the CGI-BP-S score (−1.7, P < .05) and (−1.6, P < .05) vs placebo (−0.8), respectively.

On the basis of a priori MADRS criteria, treatment with lurasidone (pooled dose ranges) vs placebo was associated with significantly higher responder rates (46.4% vs 14.8%, P = .008, number needed to treat [NNT] = 4) and remitter rates (37.5% vs 14.8%, P = .036, NNT = 5).

Adjunctive therapy study. For older adults in the adjunctive therapy study, LS mean change at week 6 for lurasidone was not significantly different from placebo on the MADRS (−13.9 vs −11.1, P = .398, effect size = 0.26;

Figure 2. Adjunctive Therapy With Lurasidone (20–120 mg/d, flexibly dosed)[a] vs Placebo: LS Mean Change in MADRS Total Score for the mITT Population[b]



[a]Effect size = 0.26.
[b]Assessed using a mixed model for repeated measures (MMRM) analysis.
Abbreviations: LS = least squares, MADRS = Montgomery-Åsberg Depression Rating Scale, mITT = modified intent-to-treat.

Table 3. Adjunctive Therapy With Lurasidone: Endpoint Change in Primary and Secondary Efficacy Measures (mITT population)

Scores	n	Baseline Mean (SD)	Endpoint Change LS Mean (SE)	*P* Value	Effect Size
MADRS total score (primary endpoint)[a]					
Lurasidone 20–120 mg/d	26	31.3 (5.4)	–13.9 (2.3)	.398	0.26
Placebo	27	29.6 (5.0)	–11.1 (2.2)		
CGI-BP-S score[a]					
Lurasidone 20–120 mg/d	26	4.6 (0.9)	–1.4 (0.3)	.159	0.43
Placebo	27	4.5 (0.6)	–0.9 (0.2)		
QIDS-SR_{16} total score[b]					
Lurasidone 20–120 mg/d	26	15.7 (3.9)	–6.1 (1.2)	.984	0.01
Placebo	27	14.6 (3.4)	–6.0 (1.2)		
HARS total score[b]					
Lurasidone 20–120 mg/d	24	14.8 (5.0)	–6.5 (1.5)	.183	0.38
Placebo	27	15.4 (5.1)	–3.5 (1.4)		
Q-LES-Q-SF score[b]					
Lurasidone 20–120 mg/d	24	38.6 (13.9)	+14.3 (3.9)	.622	0.14
Placebo	27	35.8 (11.5)	+11.5 (3.7)		
SDS total score[b]					
Lurasidone 20–120 mg/d	11	20.0 (4.5)	–7.1 (3.7)	.576	0.22
Placebo	19	19.3 (5.2)	–4.3 (3.7)		

[a]Mixed model for repeated measures analysis.
[b]Analysis of covariance—last observation carried forward analysis.
Abbreviations: CGI-BP-S = Clinical Global Impressions, Bipolar–Severity of Illness depression scale; HARS = Hamilton Anxiety Rating Scale; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; mITT = modified intent-to-treat population; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; QIDS-SR_{16} = Quick Inventory of Depressive Symptomatology–Self Report, 16 item; SDS = Sheehan Disability Scale.

Figure 2) and the CGI-BP-S score (–1.4 vs –0.9, $P = .159$, effect size = 0.43; Table 3). For the other secondary efficacy measures, LOCF-endpoint effect sizes for lurasidone ranged from 0.01 (QIDS-SR_{16}) to 0.38 (HARS); none of the secondary measures was significant for adjunctive lurasidone (Table 3).

Adjunctive treatment with lurasidone was associated with nonsignificantly different responder rates (46.2% vs 37.0%; not significant [NS]; NNT = 11) and remitter rates (38.5% vs 29.6%; NS; NNT = 12).

Safety/Tolerability

Monotherapy study. In the older patient subgroup, treatment-emergent adverse events reported with an incidence ≥ 5% in the lurasidone group and more frequent than placebo are summarized in Table 4. The most frequent adverse events reported in the lurasidone groups, 20–60 mg/d and 80–120 mg/d, respectively, were nausea (18.5% and 9.7%) and somnolence (11.1% and 0%). In addition, akathisia (9.7%) and insomnia (9.7%) were among the most

Table 4. Treatment-Emergent Adverse Events as % (Incidence ≥ 5% and > Placebo) in the Safety Population

	Monotherapy			Adjunctive Therapy With Lithium or Valproate	
Event	Lurasidone 20–60 mg/d (n = 27)	Lurasidone 80–120 mg/d (n = 31)	Placebo (n = 28)	Lurasidone 20–120 mg/d (n = 26)	Placebo (n = 27)
Nausea	18.5	9.7	14.3	7.7	11.1
Somnolence	11.1	0	3.6	0	7.4
Nasopharyngitis	7.4	0	0	0	0
Akathisia	0	9.7	3.6	19.2	0
Anxiety	7.4	0	0	0	3.7
Vomiting	7.4	0	3.6	0	0
Pruritus	7.4	0	0	0	7.4
Diarrhea	7.4	6.5	3.6	0	0
Insomnia	7.4	9.7	3.6	11.5	0
Muscle spasms	3.7	6.5	3.6	0	0
Fatigue	0	6.5	3.6	0	0
Restlessness	0	6.5	0	0	7.4
Abnormal dreams	0	0	0	7.7	3.7
Tremor	0	0	0	7.7	7.4
Any adverse event rated as "severe"	4.7	1.6	1.6	2.4	2.4

frequently reported events in the 80–120 mg/d group, with the rate of akathisia exhibiting a dose-related increase. The incidence of adverse events rated as "severe" was low in the lurasidone 20–60 mg/d (4.7%) and 80–120 mg/d (1.6%) groups and in the placebo group (1.6%). In this older adult subgroup, there was 1 possibly treatment-related serious adverse event (panic attack), which resolved; no deaths occurred.

At baseline in the monotherapy study, mean body weight was similar in the pooled lurasidone group (76.4 kg [168.4 lb]) and the placebo group (74.1 kg [163.4 lb]). Mean change in weight was also similar for the pooled lurasidone group (−0.3 kg [−0.7 lb]) and the placebo group (−0.2 kg [−0.4 lb]).

In the older patient subgroup in the monotherapy study, no clinically meaningful treatment-emergent, between-group differences in vital signs, ECG, or laboratory parameters were observed. Clinically meaningful abnormalities in metabolic parameters were defined, a priori, as a cholesterol or triglyceride level ≥ 300 mg/dL or a glucose level ≥ 160 mg/dL. A small number of patients in the older adult subgroup experienced markedly abnormal, treatment-emergent, postbaseline laboratory values in the lurasidone 20–60 mg/d, 80–120 mg/d, and placebo groups, respectively, for cholesterol (n = 1, 1, and 1), triglycerides (n = 3, 1, and 0), and glucose (n = 0, 0, and 1).

Adjunctive therapy study. In the older patient subgroup, the most frequent adverse events reported on lurasidone treatment were akathisia (19.2%) and insomnia (11.5%) (Table 4). The incidence of adverse events rated as "severe" was low in both the lurasidone (2.4%) and placebo (2.4%) groups. There were no deaths, and no treatment-related serious adverse events in the adjunctive therapy study.

At baseline in the adjunctive study, mean body weight was similar in the lurasidone group (79.4 kg [175.0 lb]) and the placebo group (78.4 kg [172.8 lb]). Mean change in weight was also similar for the lurasidone group (−1.0 kg [−2.2 lb]) and the placebo group (+0.2 kg [+0.4 lb]).

In the older patient subgroup in the adjunctive therapy study, there were no clinically meaningful treatment-emergent, between-group differences in vital signs, ECG, or laboratory parameters. A small number of patients in the older adult subgroup experienced markedly abnormal, treatment-emergent, postbaseline laboratory values in the lurasidone and placebo groups, respectively, for cholesterol (n = 1 and 1), triglycerides (n = 2 and 1), and glucose (n = 0 and 0).

DISCUSSION

In this post hoc analysis of 2 double-blind, placebo-controlled, randomized, 6-week studies, monotherapy with lurasidone significantly improved depressive symptoms compared to placebo in older adult patients with a diagnosis of bipolar depression, while improvement on lurasidone adjunctive with lithium or valproate was not significantly different from placebo.

Among older adults in the monotherapy study, efficacy was robust, with moderate-to-large effect sizes on both clinician-rated ($d = 0.83$) and patient-reported ($d = 0.51$) measures of depression symptom severity as well as on the CGI-BP-S ($d = 0.69$). Reduction in depression symptom severity was associated with modest improvement on other patient-reported measures of quality of life and functional impairment. The magnitude of improvement in depression severity on lurasidone in this older adult sample compares favorably with results for the total sample in the parent study, 83% of whom were under the age of 55 years (effect size = 0.51).[15]

Among older adults in the adjunctive therapy study, the magnitude of endpoint improvement on lurasidone in measures of depression symptom severity (MADRS, CGI-BP-S, QIDS-SR_{16}) was comparable to what was observed in older adults in the monotherapy study. However, improvement in the adjunctive lurasidone group was associated with effect sizes in the small-to-moderate range

on the primary (MADRS, $d = 0.26$) and secondary (CGI-BP-S, $d = 0.43$) endpoints. These effect sizes are comparable to the endpoint effect sizes reported for lurasidone in the parent adjunctive study (84% under age 55) on the MADRS (0.34) and CGI-BP-S (0.36).[16]

Lower treatment effect sizes are notably more frequent in adjunctive therapy studies compared to monotherapy studies.[30] Lithium and valproate each has been shown to have antidepressant effects in some patients with bipolar depression,[31] and a systematic review[32] of older adults with refractory unipolar depression suggests that augmentation with lithium is associated with an increased antidepressant response. In the current older adult analyses, response rates in the placebo group were higher with adjunctive therapy compared to monotherapy (37.0% vs 14.8%), consistent with a contribution of adjunctive lithium and valproate to placebo group response.

In the monotherapy study, the mean modal daily dose of lurasidone was approximately the same for older adults compared with younger adults (< 55 years) in the parent study for both the 20–60 mg/d group (34.6 mg vs 35.0 mg) and for the 80–120 mg/d group (96.0 mg vs 91.5 mg). In the adjunctive therapy study, the mean modal daily dose was also similar for the older and younger subgroups (76.2 mg vs 75.0 mg).

Among older adults in the monotherapy study, a dose-related increase in adverse event rates was observed only for akathisia; however, we note that the interpretation of these findings is limited by small sample sizes. Among older adults in the adjunctive therapy study, akathisia and insomnia were the most frequently reported adverse events. For older adults in both studies, the incidence of individual adverse events and discontinuation rates due to adverse events were comparable to what has previously been reported for the (predominantly) younger adults in the parent studies.[15,16]

Several limitations in the current results should be noted. First, while the study utilized a priori measures and preplanned analysis methods, this was a post hoc subgroup analysis with small sample sizes that were not powered to show significant differences. This is especially true for the adjunctive therapy study, where we calculate that we would need 312 patients per treatment group to have 90% power to detect the effect size of 0.26 as significant at an α level of .05 (2-sided test). Thus, the current findings should be considered exploratory. Second, patients with significant medical and neurologic comorbidities were excluded as per parent study criteria. Also, patients over the age of 65 years were underrepresented, comprising approximately 11% of the current analysis sample. Thus, efficacy and tolerability results may not be generalizable to a more elderly patient group than was studied here, especially where higher levels of comorbidity are present. Finally, there was an underrepresentation of nonwhite races in the treatment sample, which may limit the generalizability of the current results to minority populations.

In summary, the results of these post hoc analyses of 2 randomized, 6-week, double-blind, placebo-controlled studies in adults 55 years and older found that monotherapy with lurasidone in the dose range of 20–120 mg/d was an effective treatment for bipolar depression, while adjunctive therapy with lurasidone was not associated with significant improvement. Both monotherapy and adjunctive therapy with lurasidone were safe and well-tolerated in this older adult population. The inclusion of lithium or valproate as background treatments in the adjunctive therapy study appeared to confer antidepressant effects. Further investigation is warranted in larger, adequately powered trials to confirm these findings.

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