

It is illegal to post this copyrighted PDF on any website.

Efficacy of Lurasidone in Adults Aged 55 Years and Older With Bipolar Depression: Post Hoc Analysis of 2 Double-Blind, Placebo-Controlled Studies

Martha Sajatovic, MD^{a,*}; Brent P. Forester, MD, MSc^b; Joyce Tsai, PhD^c; Hans Kroger, MPH, MS^c; Andrei Pikalov, MD, PhD^c; Josephine Cucchiaro, PhD^c; and Antony Loebel, MD^c

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.

J Clin Psychiatry 2016;77(10):e1324–e1331
dx.doi.org/10.4088/JCP.15m10261

© Copyright 2016 Physicians Postgraduate Press, Inc.

^aCase Western Reserve University School of Medicine, Cleveland, Ohio

^bHarvard Medical School, Boston, Massachusetts; and McLean Hospital, Belmont, Massachusetts

^cSunovion Pharmaceuticals, Inc, Marlborough, Massachusetts and Fort Lee, New Jersey

*Corresponding author: Martha Sajatovic, MD, Department of Psychiatry, University Hospitals Case Medical Center, 10524 Euclid Ave, Cleveland, OH 44106 (martha.sajatovic@uhhospitals.org).

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 D₂, 5-HT_{2A}, and 5-HT₇ receptors (as an antagonist); moderate affinity for 5-HT_{1A} receptors (as a partial agonist); and no appreciable affinity for H₁ and M₁ 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 program¹⁹ 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.

- 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 Interview²⁰ 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-SR₁₆),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

It is illegal to post this copyrighted PDF on any website.

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)

^aPooled 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

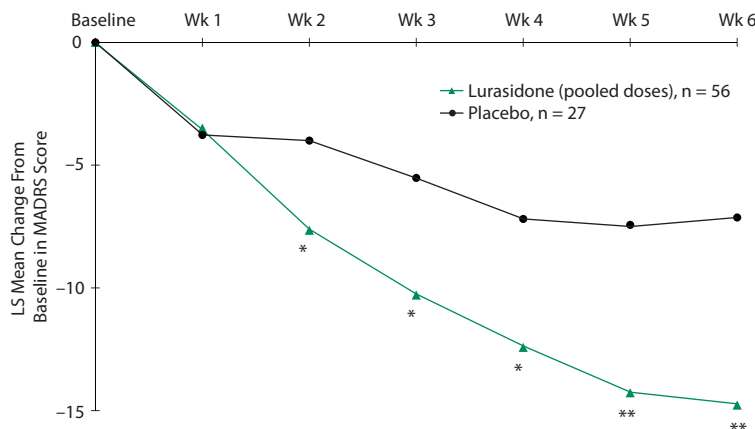
20–60 mg/d group and 96.0 mg for the 80–120 mg/d group. In the adjunctive therapy study, the mean modal daily dose of lurasidone was 76.2 mg.

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^aEffect size for pooled lurasidone dose groups = 0.81.^bAssessed 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)		

^aMixed model for repeated measures analysis.^bAnalysis 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-SR₁₆ = Quick Inventory of Depressive Symptomatology–Self Report, 16 item; SDS = Sheehan Disability Scale.

the patient-rated QIDS-SR₁₆, but it was not significant on the HARS, Q-LES-Q-SF, and SDS (Table 2).

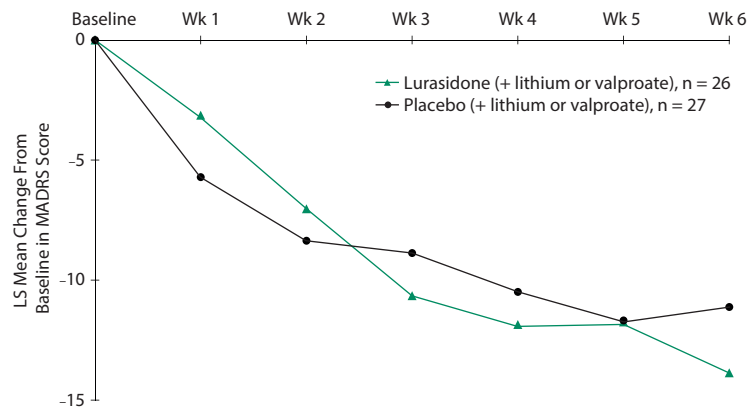
For older adults in the monotherapy study, treatment with lurasidone was associated with significantly greater week 6 improvement for each fixed-flexible daily dose range (20–60 mg/d and 80–120 mg/d) on the MADRS score (–15.4, $P < .01$) and (–14.1, $P < .05$) vs placebo (–7.1), respectively, and on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

It is illegal to post this copyrighted PDF on any website.

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



^aEffect size = 0.26.

^bAssessed 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)		

^aMixed model for repeated measures analysis.

^bAnalysis 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-SR₁₆ = 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-SR₁₆) 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 $\geq 5\%$ 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 $\geq 5\%$ and $>$ Placebo) in the Safety Population

Event	Monotherapy			Adjunctive Therapy With Lithium or Valproate	
	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-SR₁₆) 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

It is illegal to post this copyrighted PDF on any website.

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 review³² 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 alpha 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.

Submitted: July 22, 2015; accepted February 11, 2016.

Online first: August 16, 2016.

Drug names: fluoxetine/olanzapine (Symbyax); lurasidone (Latuda), quetiapine (Seroquel and others).

Potential conflicts of interest: Dr Sajatovic has received research grants from Pfizer, Merck, Ortho-McNeil-Janssen, Janssen, Reuter Foundation, Woodruff Foundation, Reinberger Foundation, National Institutes of Health, Centers for Disease Control and Prevention; is a consultant to Bracket, Prophase, Otsuka, Pfizer, Neurocrine, and Sunovion; receives royalties from Springer Press, Johns Hopkins University Press, Oxford University Press, UpToDate, and Lexicomp; and has participated in the following CME activities: American Physician Institute, MCM Education, and CMEology. Dr Forester has received grant funding from AssureRX and the Rogers Family Foundation. Drs Tsai, Pikalov, Cucchiari, and Loebel are employees of Sunovion Pharmaceuticals, Inc. Mr Kroger was an employee of Sunovion at the time this analysis was performed.

Funding/support: Sponsored by Sunovion Pharmaceuticals, Inc.

Role of the sponsor: The sponsor was involved in the study design, collection, and analysis of data. The interpretation of results and the decision to submit this manuscript for publication in *The Journal of Clinical Psychiatry* were made by the authors independently.

Previous presentation: A preliminary summary of these data was previously presented at the American Association for Geriatric Psychiatry annual meeting; March 27–30, 2015; New Orleans, Louisiana • American Psychiatric Association annual meeting; May 16–20, 2015; Toronto, Canada • American College of Neuropsychopharmacology Annual Meeting; December 7–11, 2014; Phoenix, Arizona.

Acknowledgments: The authors thank the study participants and the members of the lurasidone bipolar disorder study group. Editorial and medical writing support was provided by Edward Schweizer, MD, of Paladin Consulting Group and was funded by Sunovion Pharmaceuticals, Inc.

REFERENCES

- Kessler RC, Wang PS. The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annu Rev Public Health*. 2008;29(1):115–129.
- Sajatovic M, Chen P. Geriatric bipolar disorder. *Psychiatr Clin North Am*. 2011;34(2):319–333.
- Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59(6):530–537.
- Calabrese JR, Hirschfeld RM, Frye MA, et al. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a US community-based sample. *J Clin Psychiatry*. 2004;65(11):1499–1504.
- Depp CA, Davis CE, Mittal D, et al. Health-related quality of life and functioning of middle-aged and elderly adults with bipolar disorder. *J Clin Psychiatry*. 2006;67(2):215–221.
- Gildengers AG, Mulsant BH, Begley A, et al. The longitudinal course of cognition in older adults with bipolar disorder. *Bipolar Disord*. 2009;11(7):744–752.
- Solomon DA, Leon AC, Coryell WH, et al. Longitudinal course of bipolar I disorder: duration of mood episodes. *Arch Gen Psychiatry*. 2010;67(4):339–347.
- Fagioli A, Forgiione R, Maccari M, et al. Prevalence, chronicity, burden and borders of bipolar disorder. *J Affect Disord*. 2013;148(2–3):161–169.
- Parker G, McCraw S, Hadzi-Pavlovic D, et al. Costs of the principal mood disorders: a study of comparative direct and indirect costs incurred by those with bipolar I, bipolar II and unipolar disorders. *J Affect Disord*. 2013;149(1–3):46–55.

10. Dols A, Kupka R, Kessing LV, et al. Bipolar disorder in the elderly. *Aging Health*. 2011;7(6):797–800.
11. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079–1088.
12. Brown EB, McElroy SL, Keck PE Jr, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry*. 2006;67(7):1025–1033.
13. Tohen M, McDonnell DP, Case M, et al. Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. *Br J Psychiatry*. 2012;201(5):376–382.
14. Sanford M, Keating GM. Quetiapine: a review of its use in the management of bipolar depression. *CNS Drugs*. 2012;26(5):435–460.
15. Loebel A, Cucchiari 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(2):160–168.
16. Loebel A, Cucchiari 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(2):169–177.
17. 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(1):171–181.
18. Chiu YY, Ereshefsky L, Preskorn SH, et al. Lurasidone drug-drug interaction studies: a comprehensive review. *Drug Metabol Drug Interact*. 2014;29(3):191–202.
19. Loebel A, Xu J, Hsu J, et al. The development of lurasidone for bipolar depression. *Ann NY Acad Sci*. 2015;1358:95–104.
20. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22–33.
21. Sachs GS. Strategies for improving treatment of bipolar disorder: integration of measurement and management. *Acta Psychiatr Scand suppl*. 2004;110(422):7–17.
22. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
23. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
24. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res*. 1997;73(3):159–171.
25. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
26. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
27. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull*. 1993;29(2):321–326.
28. Sheehan DV. *The Anxiety Disease*. New York, NY: Bantam Books; 1983.
29. Chappell P, Feltner DE, Makumi C, et al. Initial validity and reliability data on the Columbia-Suicide Severity Rating Scale. *Am J Psychiatry*. 2012;169(6):662–663, author reply 663.
30. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. *CNS Spectr*. 2013;18(4):199–208.
31. Selle V, Schalkwijk S, Vázquez GH, et al. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. *Pharmacopsychiatry*. 2014;47(2):43–52.
32. Cooper C, Katona C, Lyketsos K, et al. A systematic review of treatments for refractory depression in older people. *Am J Psychiatry*. 2011;168(7):681–688.