Efficacy of Lurasidone in Antipsychotic-Naive vs. Antipsychotic-Exposed Adolescents with Schizophrenia: Post-Hoc Analysis of a Two-Year, Open-Label Study

Christoph Correll, MD[1], Michael Tocco, PhD[2], Andrei Pikalov, MD, PhD[2], Jay Hsu, PhD[2] and Robert Goldman, PhD[2]

[1]The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA; Hofstra Northwell School of Medicine, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA; and Charité Universitat Medizin, Department of Child and Adolescent Psychiatry, Berlin, Germany, and [2]Sunovion Pharmaceuticals Inc., Fort Lee, NJ and Marlborough, MA, USA

Presenting Author: Michael Tocco

Abstract

Background. Few studies have examined treatment response in adolescents with schizophrenia who are treatment-naive; and there is no placebo-controlled study that we are aware of in first episode treatment-naive patients with schizophrenia. The aim of this analysis was to evaluate the long-term efficacy of lurasidone in antipsychotic-naive adolescents with schizophrenia.

Method. Patients aged 13–17 years with schizophrenia, and a PANSS total score ≥70 and <120, were randomized to 6 weeks of double-blind (DB) treatment with lurasidone (40 or 80 mg/day) or placebo. Six-week completers were eligible to enroll in a 2-year open-label extension phase receiving lurasidone flexibly dosed from 20–80 mg/day. In a post-hoc analysis, efficacy was evaluated for 2 patient groups based on treatment status prior to entering the initial 6-week DB study (treatment naïve [TN] vs. treated previously [TP]). Treatment-naïve was defined as never having received antipsychotic treatment. Efficacy measures included the PANSS total score and the Clinical Global Impression, Severity (CGI-S) score. Level of functioning was assessed using the Children's Global Assessment Scale (CGAS), with a score of 70 representing normative levels of functioning.

Results. A total of 50 TN and 221 TP patients completed the 6-week DB study and entered the extension study; and 30 (60.0%) TN and 126 (57.0%) TP patients completed 104 weeks. During the initial 6 weeks of DB treatment, mean change in PANSS total score at endpoint was greater for lurasidone vs. placebo in both the TN group (−25.0 vs. −14.4; P<0.02; effect size, 0.75), and in the TP group (−17.3 vs. −10.0; P<0.001; effect size, 0.45). During OL extension phase treatment with lurasidone, mean change from DB baseline in the PANSS total score for TN and TP patients, at week 52 was −32.6 (n=38) and −28.1 (n=151), respectively; and at week 104 was −33.6 (n=30) and −29.2 (n=126), respectively. Mean change from DB baseline in CGI-S score at both weeks 52 and 104 was −1.8 for TN patients and −1.5 for TP patients. At DB baseline mean CGAS scores indicated significant functional impairment in both the TN and TP patients (CGAS=48 and 43, respectively). During OL treatment with lurasidone, mean change (from DB baseline) in the CGAS score at Weeks 52 and 104, respectively, was +22.0 and +22.9 in TN patients, and +21.1 and +22.9 in TP patients. During OL treatment with lurasidone, mean observed change from DB baseline in the weight (in kg,) at Weeks 52 and 104, respectively, was +4.2 and +4.8 in TN patients, and +4.0 and +5.0 in TP patients. These weight increases are consistent with expected weight gains in adolescents during a 2-year period (based on CDC growth charts).

Conclusions. In this post-hoc analysis of a 2-year study, adolescents with schizophrenia who had received no previous antipsychotic therapy showed greater improvement compared to previously treated patients during both short- and long-term treatment with lurasidone.

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Effect of Lurasidone on Manic Symptoms and Treatment-Emergent Mania in Adult and Pediatric Populations with Bipolar Depression

Michael Tocco, PhD, Andrei Pikalov, MD, PhD, Courtney Zeni, PhD and Robert Goldman, PhD

Sunovion Pharmaceuticals Inc., Fort Lee, NJ and Marlborough, MA, USA

Presenting Author: Michael Tocco

Abstract

Background. Lurasidone is approved for the treatment of bipolar depression both as monotherapy and adjunctive therapy with lithium or valproate (Li/VPA). The aim of these analyses was to evaluate the prevalence of treatment-emergent mania (TEM) and worsening of mania symptom severity in clinical trials of both adult and pediatric patients with bipolar depression treated with lurasidone.

Method. In these post-hoc analyses, TEM and change in manic symptom severity as measured by the Young Mania Rating Scale (YMRS) were evaluated in two double-blind (DB), 6-week studies in adults of lurasidone monotherapy, 20–60 mg/d (n=161) and 80–120 mg/d (n=162) vs. placebo (n=162), and adjunctive therapy of lurasidone 20–120 mg/d + Li/VPA (n=179) vs. placebo + Li/VPA (n=161). Prevalence of TEM was also evaluated in a 6-month, open-label (OL) extension study of adults treated with lurasidone monotherapy (n=316) or adjunctive therapy (n=497). In pediatric patients (ages 10–17) TEM and change in manic symptoms was evaluated in a DB 6-week study of lurasidone monotherapy (n=173) vs. placebo (n=170) and in a 24-month OL extension study. TEM was defined as an adverse event of mania or hypomania and/or having a YMRS score =16 at 2 consecutive post-baseline weekly visits (or the final assessment) in short-term studies or 1 post-baseline monthly visit in long-term studies.

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Results. Adult studies: In short-term studies, TEM rates were comparable in patients treated with lurasidone monotherapy 20–60 mg/d (3.7%) and 80–120 mg/d (1.9%) vs. placebo (1.9%). TEM rates were also comparable in patients treated with lurasidone 20–120 mg/d (1.1%) adjunctive to Li/VPA vs. placebo + Li/VPA (1.2%). In the monotherapy study, significant reduction in YMRS score was observed at study endpoint for the 20–60 mg/d group compared to placebo (−1.9 vs. −1.3; $p<0.05$) with similar improvement relative to placebo in the 80–120 mg/d group. Change for YMRS score was comparable for lurasidone and placebo in the adjunctive study. In long-term studies, 1.3% of adult patients treated with lurasidone monotherapy (n=316) met criteria for mania, and 3.8% of patients on adjunctive lurasidone therapy (n=497) met TEM criteria. Pediatric studies: TEM rates were comparable in patients treated with lurasidone vs. placebo (1.7% vs. 2.3%). LS mean reduction in symptoms of mania from baseline to week 6 was significantly greater for lurasidone vs. placebo on YMRS score (−2.0 vs. −1.1; $p<0.05$). Pediatric long-term studies: After two years of OL treatment with lurasidone, 5.2% of patients met TEM criteria. Mean change in YMRS total score from DB baseline to Month 24 continued to improve (−2.0).
Conclusions. Short-term and long-term treatment with lurasidone demonstrated significant improvement in manic symptoms and was not associated with an increased risk of TEM in either adult or pediatric patient populations compared to rates reported in clinical populations of patients.
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Long-Term Effectiveness of Lurasidone in Pediatric Bipolar Depression: Response, Remission and Recovery

Manpreet Singh, MD[1], Michael Tocco, PhD[2], Edward Schweizer, MD[3] and Andrei Pikalov, MD, PhD[2]

[1]Stanford University, Stanford Pediatric Mood Disorders Program, Stanford, CA, USA, [2]Sunovion Pharmaceuticals Inc., Marlborough, MA, USA, and [3]Paladin Consulting Group, Princeton, NJ, USA

Presenting Author: Michael Tocco

Abstract

Background. Bipolar disorder frequently has an early onset, with an estimated 1.8% prevalence of bipolar I disorder in children and adolescents. Childhood onset of bipolar disorder is typically associated with a chronic, severe, and disabling course of illness. Relatively few prospective studies are available that evaluate the long-term efficacy of atypical antipsychotics in achieving and sustaining response or remission in pediatric patients with bipolar depression. Lurasidone has been approved by the FDA as monotherapy for bipolar depression in pediatric patients ages 10–17 years. The aim of the current post-hoc analysis was to evaluate the long-term efficacy of lurasidone in achieving response or remission in children and adolescents with bipolar depression followed over a two-year period.
Method. Patients 10–17 years with bipolar I depression who completed a 6-week double-blind (DB) study of lurasidone vs. placebo were eligible to enroll in a two-year, open-label (OL) extension study in which patients were continued on flexibly-dosed lurasidone (20–80 mg/d) or switched from placebo to lurasidone. Efficacy measures included the Children's Depression Rating Scale, Revised (CDRS-R) and the Clinical Global Impression, Bipolar Depression Severity scale (CGI-BP-S). Functioning was evaluated utilizing the Clinician-rated Children's Global Assessment Scale (CGAS) score, with a score >70 indicating no clinically meaningful functional impairment. Responder criteria were met if a patient achieved criteria = 50% reduction from DB baseline in the CDRS-R total score: remission criteria were met if a patient achieved a CDRS-R Total Score =28 and a YMRS total score =8 and CGI-BP-S depression score =3, and a patient was considered to have met recovery criteria if they achieved remission with a CGAS score >70. In addition, a more stringent outcome, sustained remission, was also analyzed, which required a patient to meet remission criteria for =24 consecutive weeks.
Results. A total of 306 patients completed the 6-week DB study and entered the extension study; 195 (63.7%) patients completed one year of treatment and 168 (54.9%) patients completed two years of treatment. Responder rates at OL baseline, one year, and two years were: 51.0%, 88.4% and 91.1%, respectively; remission rates were 24.3%, 61.3%, and 75.6%, respectively; and recovery rates were 17.7%, 53.8%, and 73.8%. On a Pearson correlation analysis, there was a strong inverse relationship ($r = -0.71$) between CDRS-R total score, and global functioning as measured by the CGAS. Sustained remission was achieved by 37.2% of patients at one year and 57% of patients after two years.
Conclusions. In children and adolescents with bipolar depression, up to 2 years of treatment with lurasidone was associated with continued improvement in depressive symptoms, resulting in progressively higher rates of response, remission, recovery, and the more rigorously calculated outcome of sustained remission.
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Safety and Effectiveness of SEP−363856 in Schizophrenia: Results of a 6-Month, Open-Label Extension Study

Christoph U. Correll, MD[1], Kenneth S. Koblan, PhD[2], Seth C. Hopkins, PhD[2], Justine Kent, MD[2], Hailong Cheng, PhD[2], Robert Goldman, PhD[2] and Antony Loebel, MD[2]

[1]The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA; Hofstra Northwell School of Medicine, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA; and Charité Universitat Medizin, Department of Child and Adolescent Psychiatry, Berlin, Germany, and [2]Sunovion Pharmaceuticals Inc., Marlborough, MA, USA

Presenting Author: Kenneth S. Koblan

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