Article

Lurasidone in the Treatment of Schizophrenia: A Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study

Herbert Y. Meltzer, M.D.

Josephine Cucchiaro, Ph.D.

Robert Silva, Ph.D.

Masaaki Ogasa, M.S.

Debra Phillips

Jane Xu, Ph.D.

Amir H. Kalali, M.D.

Edward Schweizer, M.D.

Andrei Pikalov, M.D., Ph.D.

Antony Loebel, M.D.

Objective: The study was designed to evaluate the short-term efficacy and safety of lurasidone in the treatment of acute schizophrenia.

Method: Participants, who were recently admitted inpatients with schizophrenia with an acute exacerbation of psychotic symptoms, were randomly assigned to 6 weeks of double-blind treatment with 40 mg of lurasidone, 120 mg of lurasidone, 15 mg of olanzapine (included to test for assay sensitivity), or placebo, dosed once daily. Efficacy was evaluated using a mixed-model repeated-measures analysis of the change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score (as the primary efficacy measure) and Clinical Global Impressions severity (CGI-S) score (as the key secondary efficacy measure).

Results: Treatment with both doses of lurasidone or with olanzapine was associated with significantly greater improvement at week 6 on PANSS total score, PANSS positive and negative subscale scores, and CGI-S score compared with placebo. There was no statistically significant difference in mean PANSS total or CGI-S change scores for the lurasidone groups compared with the olanzapine group. With responders defined as those with an improvement of at least 20% on the PANSS, endpoint responder rates were significant compared with placebo for olanzapine only. The incidence of akathisia was higher with 120 mg of lurasidone (22.9%) than with 40 mg of lurasidone (11.8%), olanzapine (7.4%), or placebo (0.9%). The proportion of patients experiencing ≥7% weight gain was 5.9% for the lurasidone groups combined, 34.4% for the olanzapine group, and 7.0% for the placebo group.

Conclusions: Lurasidone was an effective treatment for patients with acute schizophrenia. Safety assessments indicated a higher frequency of adverse events associated with 120 mg/day of lurasidone compared with 40 mg/day.

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Atypical antipsychotic drugs generally share more potent antagonism for 5-HT_{2A} than dopamine D_2 receptors (1, 2). However, there are significant differences among these agents in their relative affinities for 5-HT_{1A}, 5-HT_{2C}, 5-HT_7, alpha-adrenergic, histamine H_1, muscarinic, and other receptors that may affect their efficacy and tolerability (2). Genetic polymorphisms in receptor proteins, as well as in cytochrome P450 isoenzymes, contribute additional between-drug variability in clinical effect (3). Thus, atypical antipsychotics do not produce uniform clinical responses in all patients, and it remains important to have multiple antipsychotic drug treatment choices to address unmet therapeutic needs in patients with schizophrenia and other psychotic disorders (4, 5).

Lurasidone is a novel psychotropic agent that has been shown in studies of cloned human receptors to be an antagonist at the 5-HT_{2A} receptor, with a binding affinity (Ki; the dissociation constant of the inhibitor) of 0.47, and a Ki of 0.99 at the D2 receptor. It also has a very high affinity for the 5-HT_7 receptor (Ki, 0.49), which is nearly identical to its affinity for the 5-HT_{2A} receptor. In addition, lurasidone has moderate partial agonist effects at the 5-HT_{1A} receptor (Ki, 6.4) and moderately potent antagonist effects at α_{2C} receptor subtypes (Ki, 10.8) (6).

In a double-blind, placebo-controlled phase 2 clinical trial (7), lurasidone demonstrated efficacy in schizophrenia at a fixed daily dose of 80 mg.

The primary objective of this phase 3 study was to evaluate the efficacy of two dosages of lurasidone (40 and 120 mg/day) compared with placebo in the treatment of patients suffering from an acute exacerbation of chronic schizophrenia. The key secondary objective was to evaluate the efficacy of lurasidone compared with placebo in improving the Clinical Global Impressions severity (CGI-S) score. Another major secondary objective was to evaluate the safety and tolerability of the 40 mg and 120 mg doses of lurasidone during 6 weeks of treatment.

Method

This was a prospective, multicenter, parallel-group study in which recently admitted acutely ill inpatients with schizophrenia with an acute exacerbation of psychotic symptoms were

This article provides Clinical Guidance (p. 967)

randomly assigned to receive 6 weeks of double-blind treatment with once-daily doses of 40 mg or 120 mg of lurasidone, 15 mg of olanzapine (included to establish assay sensitivity), or placebo. The study was conducted between January 31, 2008, and June 16, 2009, enrolling a total of 478 patients at 25 sites in the United States (N=286), five in Colombia (N=48), four in Lithuania (N=29), and 18 in Asia (India, 14 sites [N=89]; Philippines, four sites [N=26]).

All patients who entered the trial reviewed and signed an informed consent document explaining study procedures and potential risks before study entry. The study protocol and all related forms and amendments were approved by an independent ethics committee associated with each study center. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practices guidelines and with the ethical principles of the Declaration of Helsinki. An independent data and safety monitoring board reviewed unblinded safety and clinical outcome data.

Entry Criteria

Hospitalized male and female patients 18–75 years of age who met DSM-IV criteria for a primary diagnosis of schizophrenia as determined by the Mini International Neuropsychiatric Interview (8) were enrolled. Patients were also required to have an illness duration of at least 1 year and to have been hospitalized for ≤2 weeks for an acute exacerbation of psychotic symptoms and, at the screening and baseline visits, to have a CGI-S score ≥4 (moderate or greater) and a Positive and Negative Syndrome Scale (PANSS) total score ≥80, including a score ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness.

Study Medication

All study medication was identically overencapsulated to preserve the double-blind. A unique participant number was assigned by interactive voice response system when a patient entered the screening phase. At baseline (day 0), patients who continued to meet all study inclusion criteria were randomly assigned via interactive voice response system (in a 1:1:1:1 ratio) to one of four treatment arms: lurasidone, 40 mg; lurasidone, 120 mg; olanzapine, 15 mg; or placebo. Study medication was administered in the morning with a meal or within 30 minutes after eating. Participants assigned to receive lurasidone started treatment at their target dose; patients assigned to olanzapine treatment received 10 mg on days 1–7 and 15 mg thereafter. The olanzapine dosage of 15 mg/day was selected because it is widely used and because there is substantial evidence that it is an effective dosage in patients with schizophrenia, with little evidence that higher dosages offer additional efficacy advantages (9, 10). This dosage is also consistent with the olanzapine package insert (http://pi.lilly.com/us/zyprexa-pi.pdf), which states that efficacy in schizophrenia has been demonstrated in a dosage range of 10–15 mg/day, with higher doses not demonstrated to be more efficacious.

Limited use of benzodiazepines was permitted for severe anxiety, agitation, or insomnia. Participants were eligible for hospital discharge to a stable residence after 21 days of treatment if they had a CGI-S score ≤3.

Assessments

The screening evaluation consisted of the Mini International Neuropsychiatric Interview, medical and psychiatric histories, a physical examination, measurement of vital signs, ECG, and laboratory tests.

Efficacy was assessed using the PANSS total and subscale scores (including a post hoc analysis of a modified version of the cognitive subscale, consisting of items P2, N5, N7, G10, G11) (11, 12), the CGI-S, and the Montgomery-Åsberg Depression Rating Scale (MADRS; 13). PANSS and CGI-S evaluations were performed at the screening and baseline visits and, during treatment, on day 4 and at each of weeks 1 through 6. The MADRS was administered at the screening and baseline visits and at weeks 3 and 6.

Extrapyramidal symptoms were assessed with the Simpson-Angus Rating Scale (14), the Barnes Rating Scale for Drug-Induced Akathisia (15), and the Abnormal Involuntary Movement Scale (16). Safety evaluations included vital signs, weight, laboratory tests (including fasting lipids, glucose, glycosylated hemoglobin [HbA_{1c}], and insulin), 12-lead ECG, and reported adverse events. Insulin resistance and beta-cell function were measured using the homeostasis model assessment for insulin resistance (HOMA-IR) method (17).

Statistical Methods

A power calculation was performed that incorporated Bonferroni's procedure for controlling pairwise differences with placebo and was obtained via computer simulations. Assuming that lurasidone differed from placebo in the change from baseline in PANSS total score by 6.8 and 10.0 for the 40 and 120 mg/day dosages, respectively, and further assuming a standard deviation of 19.1, we calculated that 120 patients per group would provide 97% power (at an alpha level of 0.05, two-sided test) to reject the null hypothesis of no difference between placebo and at least one of the lurasidone dosage groups.

The primary efficacy analysis was performed on the intent-to-treat sample, which consisted of all participants assigned to a treatment group who received at least one dose of study medication, had a baseline PANSS assessment, and had at least one post-baseline PANSS assessment during the 6-week study. The primary efficacy measure was the change from baseline in PANSS total score at week 6, and the key secondary efficacy measure was the change from baseline in CGI-S score at week 6. Both measures were evaluated by a mixed-model repeated-measures analysis with an unstructured covariance matrix. The model included factors for pooled center, time (including all scheduled postbaseline assessment visits as a categorical variable), baseline PANSS total score or CGI-S score, treatment, and treatment-by-time interaction. The p values for the comparison of each lurasidone group with the placebo group at week 6 on change from baseline in PANSS total score and CGI-S score were adjusted for multiple comparisons using the Hommel-based tree-gatekeeping procedure to control the family-wise type I error rate (18). The olanzapine treatment group, which was included to confirm the assay sensitivity of the study, was compared with placebo using the same mixed-model repeated-measures model, without the multiple comparison adjustment. A post hoc mixed-model repeated-measures analysis of the PANSS total score and CGI-S score was also performed comparing the 40 mg and 120 mg lurasidone treatment groups to the olanzapine treatment group.

A prespecified secondary analysis was conducted for change in PANSS total score and CGI-S score, using an analysis of covariance (ANCOVA) model.

Secondary efficacy measures, including PANSS subscale scores (positive, negative, and general psychopathology) and MADRS total score, were evaluated using similar mixed-model repeated-measures models. A post hoc analysis of the modified PANSS cognitive subscale was also performed. Participants who had an improvement of at least 20% from baseline in PANSS total score at week 6 endpoint (last observation carried forward) were defined as "responders." A logistic regression was performed using the responder outcome as the dependent variable, treatment as a categorical factor, and baseline PANSS total score as a covariate.

The Cohen's d effect size was calculated for week 6 efficacy measures as the between-treatment difference score divided by the pooled standard deviation. For adverse events, number need-

TABLE 1. Baseline Characteristics of Patients With Schizophrenia in a 6-Week Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study of Lurasidone

Characteristic[a]	Treatment Group							
	Lurasidone, 40 mg (N=119)		Lurasidone, 120 mg (N=118)		Olanzapine, 15 mg (N=122)		Placebo (N=114)	
	N	%	N	%	N	%	N	%
Male	93	78	93	79	95	78	88	77
Race								
White	44	37	48	41	41	34	36	32
Black	39	33	36	31	44	36	41	36
Asian	31	26	27	23	30	25	27	24
Other	5	4	7	6	7	6	10	9
Hispanic/Latino ethnicity	23	19	19	16	17	14	16	14
≥4 previous hospitalizations	51	43	64	54	58	48	53	46
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	37.7	11.0	37.9	11.2	38.3	10.2	37.0	11.3
Age at onset of illness (years)	23.9	8.3	22.7	8.8	24.7	7.8	23.9	8.0
Duration of illness (years)	13.3	9.9	14.7	11.0	13.2	10.9	12.6	9.6
Duration of current episode (days)	33.9	15.3	33.0	12.9	33.5	14.5	35.6	16.8
PANSS total score	96.6	10.7	97.9	11.3	96.3	12.2	95.8	10.8
CGI severity score	5.0	0.7	5.0	0.6	4.9	0.7	4.9	0.7
MADRS total score	10.8	7.0	11.4	7.2	10.8	6.2	10.6	6.1

[a] PANSS=Positive and Negative Syndrome Scale; CGI=Clinical Global Impressions scale; MADRS=Montgomery-Åsberg Depression Rating Scale.

ed to harm was calculated as 1 divided by the difference in the risk of an adverse event for active drug compared with placebo.

Significance testing of selected safety parameters was performed based on a nonparametric rank ANCOVA with baseline value as a covariate, not adjusted for multiple comparisons.

Results

Of a total of 781 patients who were screened and entered the washout period, 478 were randomly assigned to 6 weeks of double-blind treatment (Figure 1). Baseline demographic and clinical characteristics were comparable among the four treatment groups (Table 1). The proportion of patients in the lurasidone 40 mg group who completed the study treatment (64.2%) was similar to the proportions who completed treatment in the placebo group (61.2%) and the olanzapine group (68.3%); a somewhat lower proportion of patients in the lurasidone 120 mg group completed the study treatment (55.5%) (Figure 1).

Efficacy

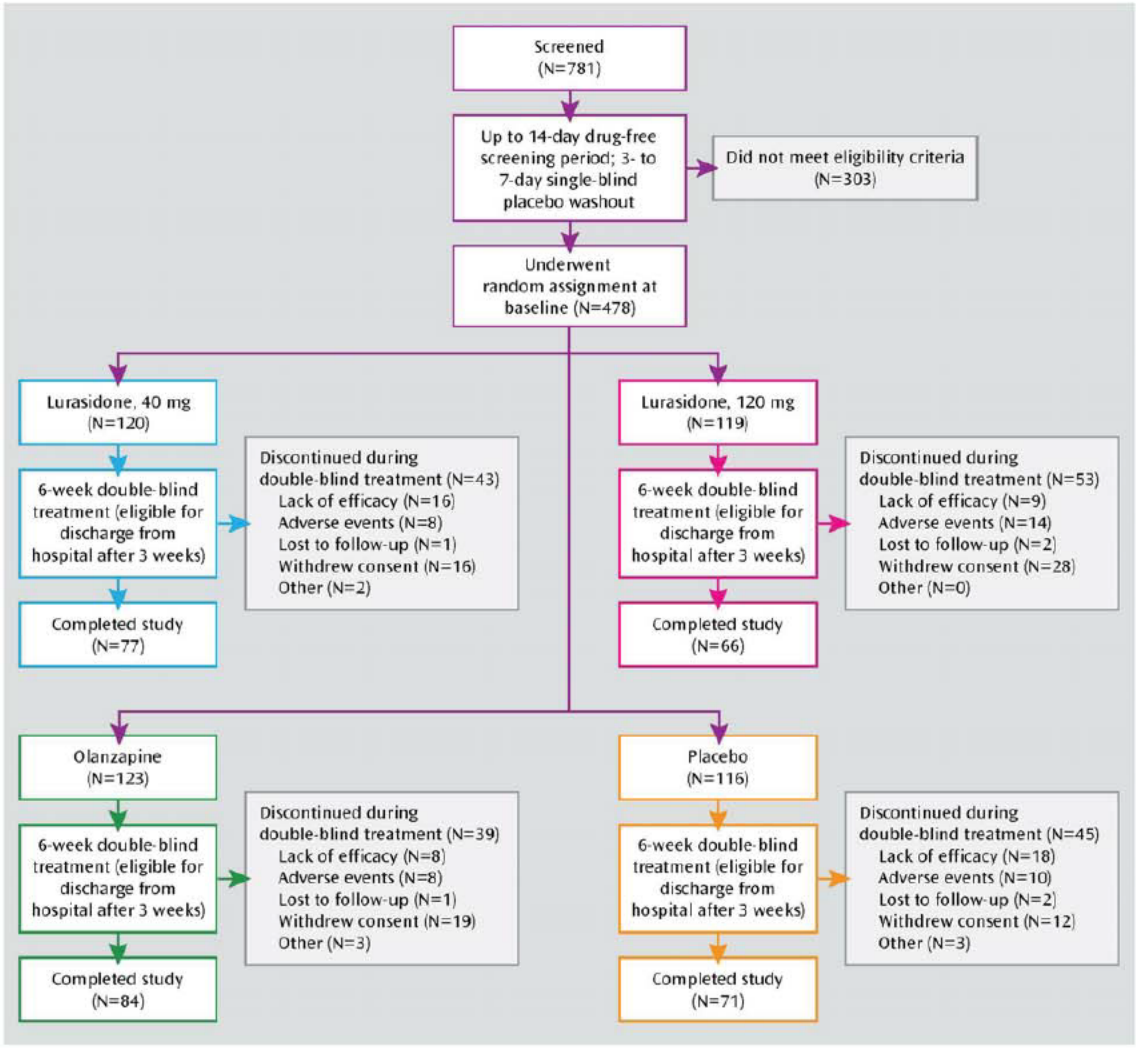
Based on the mixed-model repeated-measures analysis, the change from baseline to week 6 in PANSS total score was significantly greater for the lurasidone 40 mg (–25.7; adjusted p=0.002) and 120 mg (–23.6; adjusted p=0.022) groups compared with the placebo group (–16.0) (Table 2). The change in PANSS total score was also significantly greater for the olanzapine group (–28.7, p<0.001), thus confirming the assay sensitivity of the study. Statistically significant separation from placebo on the PANSS total score was observed from week 1 onward for the lurasidone 40 mg and olanzapine groups, and from week 3 onward for the lurasidone 120 mg group (Figure 2; see also Table S1 in the online data supplement). Treatment with both dosages of lurasidone and with olanzapine was also associated with significantly greater improvement at week 6 compared with placebo on the PANSS positive, negative, and general psychopathology subscale scores (Table 2; see also Table S1 in the online data supplement). Based on a post hoc analysis, treatment with both dosages of lurasidone, as well as with olanzapine, was also associated with significantly greater improvement at week 6 on the modified PANSS cognitive subscale score (see Table 2).

For the CGI-S score, the change from baseline to week 6 was also significantly greater for the lurasidone 40 mg (–1.5; adjusted p=0.011) and 120 mg (–1.4; adjusted p=0.040) groups compared with the placebo group (–1.1; see Table 2). The change in CGI-S score was also significantly greater for the olanzapine group (–1.5; p<0.001). Statistically significant separation from placebo on the CGI-S was observed from week 1 onward for the lurasidone 120 mg group, and from week 2 onward for the lurasidone 40 mg group and the olanzapine group compared with the placebo group (see Table S1 and Figure S1 in the online data supplement).

In a post hoc mixed-model repeated-measures analysis of PANSS total score and CGI-S score, there was no statistically significant difference in least-squares mean change scores at week 6 for the olanzapine group compared with either lurasidone group.

In a secondary analysis, an ANCOVA was performed on change from baseline to week 6 (last observation carried forward) for PANSS total score and CGI-S score. In this analysis, the least-squares mean change in PANSS total score was significantly greater for the lurasidone 40 mg (–23.1, p=0.001; effect size, 0.43) and 120 mg (–20.0, p=0.049; effect size, 0.26) groups compared with the place-

FIGURE 1. Flow of Patients With Schizophrenia in a Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study of Lurasidone



bo group (–15.2). Similarly, the least-squares mean change in PANSS total score was also significantly greater for the olanzapine group (–26.7, p<0.001). In an ANCOVA analysis of CGI-S score, least-squares mean change at week 6 (last observation carried forward) was significantly greater for the lurasidone 40 mg group compared with the placebo group (–1.2, p=0.012), but the comparison with the placebo group was not significant for the lurasidone 120 mg group. The least-squares mean change in CGI-S score was significant for the olanzapine group (–1.4, p<0.001). The results of these sensitivity analyses for PANSS total score and CGI-S score were similar to, and support, the results of the primary mixed-model repeated-measures analysis. Furthermore, on a pairwise comparison, there were no significant differences in endpoint change between the two lurasidone groups on PANSS total score or CGI-S score.

In a logistic regression analysis, responder rates (compared with placebo) and associated odds ratios at 6 weeks (last observation carried forward) were not significant for either of the lurasidone groups, but the comparison was significant for the olanzapine group (a responder rate of 74%, compared with a rate of 49% for placebo; odds ratio=2.9, p<0.001).

Improvement on the MADRS at week 6 was not significantly different between either of the lurasidone groups and the placebo group, whereas the olanzapine group showed significantly greater improvement compared with the placebo group (Table 2; see also Figure S2 in the online data supplement).

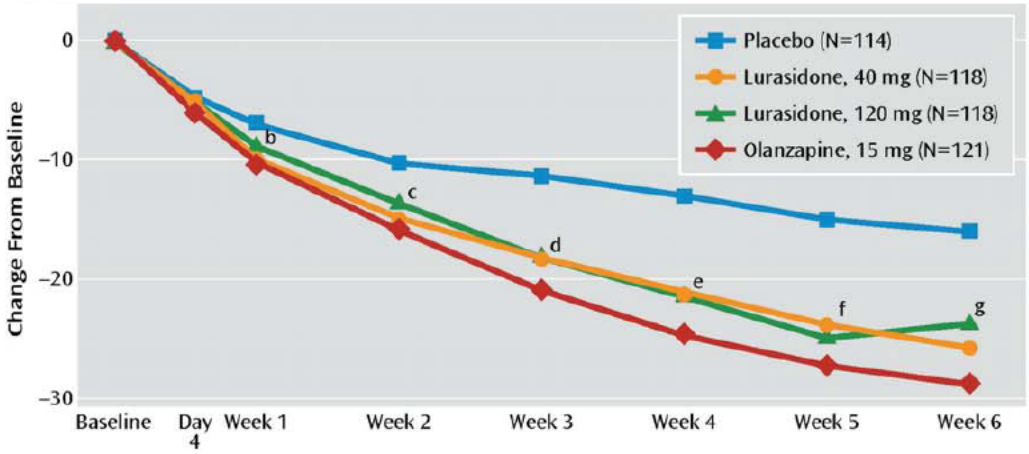
The ANCOVA subgroup analyses showed no significant treatment interactions by gender, race, ethnicity, region, or age for either the PANSS total score or the CGI-S score.

TABLE 2. Change From Baseline to Week 6 on Efficacy Measures for Patients With Schizophrenia in a Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study of Lurasidone[a]

	Treatment Group										
	Lurasidone, 40 mg (N=118)			Lurasidone, 120 mg (N=118)			Olanzapine, 15 mg (N=121)			Placebo (N=114)	
Measure[b]	Estimate	SE	p[c]	Estimate	SE	p[c]	Estimate	SE	p[c]	Estimate	SE
PANSS											
Total score change[d]	−25.7	2.0	<0.001	−23.6	2.1	0.011	−28.7	1.9	<0.001	−16.0	2.1
Positive subscale score change	−7.7	0.7	0.018	−7.5	0.7	0.035	−9.3	0.7	<0.001	−5.4	0.7
Negative subscale score change	−6.0	0.5	0.002	−5.2	0.6	0.045	−6.2	0.5	<0.001	−3.6	0.5
General psychopathology score change	−12.4	1.0	0.001	−11.1	1.0	0.022	−13.3	0.9	<0.001	−7.8	1.0
Cognitive subscale (modified) score change	−4.2	0.3	0.005	−4.0	0.4	0.012	−4.6	0.3	<0.001	−2.7	0.4
CGI severity score change[e]	−1.5	0.1	0.006	−1.4	0.1	0.040	−1.5	0.1	<0.001	−1.1	0.1
MADRS total score change	−3.5	0.5	0.324	−3.2	0.6	0.571	−5.0	0.5	0.003	−2.8	0.6

[a] Change was assessed using a mixed-model repeated-measures analysis.
[b] PANSS=Positive and Negative Syndrome Scale; CGI=Clinical Global Impressions scale; MADRS=Montgomery-Åsberg Depression Rating Scale.
[c] Compared with placebo group; p values are unadjusted and are based on a repeated-measures linear regression model of the change from baseline score, with fixed effects for pooled center, assessment visit as a categorical variable, baseline score, treatment, and treatment-by-assessment visit interaction, assuming an unstructured covariance matrix.
[d] For total score change on the PANSS, the adjusted p values (using the Hommel-based tree-gatekeeping procedure) for the lurasidone 40 mg and 120 mg groups compared with the placebo group were 0.002 and 0.022, respectively. For each of the lurasidone groups compared with the olanzapine group, unadjusted p values were nonsignificant.
[e] For CGI severity score change, the adjusted p values (using the Hommel-based tree-gatekeeping procedure) for the lurasidone 40 mg and 120 mg groups compared with the placebo group, were 0.011 and 0.040, respectively. For each of the lurasidone groups compared with the olanzapine group, unadjusted p values were nonsignificant.

FIGURE 2. Change From Baseline in PANSS Total Score in a Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study of Lurasidone[a]



[a] Statistical significance was computed on the basis of a repeated-measures linear regression model of the change from baseline score, with fixed effects for pooled site, assessment visit as a categorical variable, baseline score, treatment, and treatment-by-assessment visit interaction, assuming an unstructured covariance matrix; p values are unadjusted, and only significant p values are noted.
[b] Week 1 comparison with placebo: p=0.022 for lurasidone 40 mg; p=0.008 for olanzapine.
[c] Week 2 comparison with placebo: p=0.008 for lurasidone 40 mg; p=0.002 for olanzapine.
[d] Week 3 comparison with placebo: p=0.002 for lurasidone 40 mg; p=0.004 for lurasidone 120 mg; p<0.001 for olanzapine.
[e] Week 4 comparison with placebo: p<0.001 for lurasidone 40 mg; p<0.001 for lurasidone 120 mg; p<0.001 for olanzapine.
[f] Week 5 comparison with placebo: p=0.001 for lurasidone 40 mg; p<0.001 for lurasidone 120 mg; p<0.001 for olanzapine.
[g] Week 6 comparison with placebo: p<0.001 for lurasidone 40 mg; p=0.011 for lurasidone 120 mg; p<0.001 for olanzapine.

Safety

Adverse events. A comparable proportion of patients in the lurasidone 40 mg group and in the placebo group reported experiencing at least one adverse event (Table 3); the incidence was somewhat higher in the lurasidone 120 mg group and the olanzapine group. The majority of adverse events in all treatment groups were rated as mild to moderate. Rates of discontinuations due to adverse

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