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Original article

Efficacy of lurasidone across five symptom dimensions of schizophrenia: Pooled analysis of short-term, placebo-controlled studies

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ABSTRACT

Objective: To evaluate the efficacy of lurasidone for schizophrenia using an established five-factor model of the Positive and Negative Syndrome Scale (PANSS).
Methods: Patient-level data were pooled from five randomized, double-blind, placebo-controlled, 6-week studies of lurasidone (fixed doses, 40–160 mg/d) for patients with an acute exacerbation of schizophrenia. Changes in five established PANSS factors were assessed using mixed-model repeated measures analysis.
Results: Compared with placebo ($n = 496$), lurasidone ($n = 1029$, dose groups pooled) significantly improved the PANSS total score at Week 6 (−22.6 vs. −12.8; $P < 0.001$; effect size, 0.45), as well as all factor scores ($P < 0.001$ for each): positive symptoms (−8.4 vs. −6.0; effect size, 0.43), negative symptoms (−5.2 vs. −3.3; effect size, 0.33), disorganized thought (−4.9 vs. −2.8; effect size, 0.42), hostility/excitement (−2.7 vs. −1.6; effect size, 0.31), and depression/anxiety (−3.2 vs. −2.3; effect size, 0.31). Separation from placebo occurred at Week 1 for the positive symptoms, disorganized thought, and hostility/excitement factors and at Week 2 for the other factors.
Conclusions: In this pooled analysis of short-term studies in patients with acute schizophrenia, lurasidone demonstrated significant improvement for each of the five PANSS factor scores, indicating effectiveness across the spectrum of schizophrenia symptoms.

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1. Introduction

Schizophrenia is a heterogeneous disorder characterized by symptoms that cut across multiple domains, such as perception, mood, cognition, and behavior [1]. These symptoms are frequently debilitating [61,65], leading to chronic impairment in social and vocational functioning [14,26,63]. Early conceptualizations comprised positive (e.g., hallucinations, delusions, thought disorder, and disorganized behavior) and negative (e.g., blunted affect, poverty of speech, and avolition) symptoms [3,10], but did not account for the full range of symptomatology associated with schizophrenia [4,30,31,37,40,47].

Comprehensive evaluation of clinical improvement across a broad range of symptom domains relevant to functional status and long-term outcome may be facilitated by Positive and Negative Syndrome Scale (PANSS) factor analysis [11,24]. Five-factor solutions of the PANSS have emerged as providing the most complete and even "consensus" descriptions of the major symptomatic components of schizophrenic illness [28,30,32,37,62]. The composition of factors varies somewhat across studies, primarily as a result of differences in the factor loading of a small number of individual PANSS items, and there is ongoing debate in the literature as to which five-factor model is most useful in clinical practice [20]. However, similar symptom clusters or factors have been consistently identified across studies in patients with schizophrenia: positive symptoms, negative symptoms, disorganized thought, hostility/excitement, and depression/anxiety [8,11,27,30,37,58,62].

Lurasidone[1] is an atypical antipsychotic that has high affinity for D_2, 5-hydroxytryptamine 2A (5-HT_{2A}), and 5-HT_7 receptors (where it acts as an antagonist), and moderate affinity for 5-HT_{1A}

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[1] 40 mg, 80 mg, 120 mg, and 160 mg lurasidone hydrochloride is equivalent to 37 mg, 74 mg, 111 mg, and 148 mg lurasidone (active ingredient without salt), respectively.

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(partial agonist) and α_{2C} receptors (antagonist) [18]. Randomized, placebo-controlled studies have demonstrated the efficacy of lurasidone in the treatment of schizophrenia [34,38,39,42,44] and bipolar depression (both as monotherapy and as adjunct treatment to lithium or valproate) [35,36]. Lurasidone is licensed by the European Medicines Agency for the treatment of schizophrenia and approved by the US Food and Drug Administration for the treatment of schizophrenia as well as major depressive episodes associated with bipolar I disorder (bipolar depression). Improvements in cognitive functioning in patients with schizophrenia treated with lurasidone have been shown [15,16], and a pooled analysis of short-term data found reductions in depressive symptomatology in patients with schizophrenia who received lurasidone [41]. The objective of the present post-hoc analysis was to evaluate the efficacy of lurasidone across the spectrum of symptoms of schizophrenia using a previously established five-factor model of the PANSS [37].

2. Subjects and methods

2.1. Study design

Patient-level data were pooled from five similarly designed, 6-week, randomized, double-blind, placebo-controlled, fixed-dose studies that demonstrated the efficacy of lurasidone in the treatment of patients experiencing an acute exacerbation of schizophrenia (Fig. 1). Two short-term lurasidone studies (study 049 and study 1002) were excluded from the analysis because they were failed studies in which neither lurasidone, nor established antipsychotic medications (haloperidol and risperidone) used as active comparators, separated from placebo on standard measures of efficacy. Studies 1 and 2 were phase II studies conducted in the United States between February 2001 and December 2004, using the Brief Psychiatric Rating Scale (BPRS) [45] derived from the PANSS [25] as the primary outcome measure, with the Clinical Global Impression-Severity (CGI-S) [13] as a secondary measure. Studies 3–5 were multinational, phase III studies conducted between October 2007 and June 2010, which utilized the PANSS total score as the primary endpoint, with the CGI-S as a key secondary outcome. For the purposes of this analysis, PANSS data were pooled across studies. Fixed doses of lurasidone in these studies were 40 mg/d, 80 mg/d, 120 mg/d, or 160 mg/d; olanzapine and quetiapine XR were used in one study each as active comparators, but are not included in the present analyses.

The study design, methods, and primary results for each study included in this analysis have been published elsewhere [34,38,39,42,44], and therefore only key details are summarized here. Inclusion/exclusion criteria were similar across the five studies. Patients were adults, aged 18–75 years, with a diagnosis of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, 4th edition [DSM-IV]) for at least 1 year and were experiencing an acute exacerbation of psychotic symptoms. Patients were required to have a CGI-S score ≥ 4 (moderate or greater) and a PANSS total score ≥ 80, including a score ≥ 4 (moderate) on two or more on the following five items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness.[2] Exclusion criteria included an acute or unstable medical condition, evidence of any other chronic disease of the central nervous system, alcohol or other drug abuse/dependence within the past 3–6 months, or evidence of a severe movement disorder.

2.2. Study procedures

All patients provided written informed consent prior to study enrollment. Study conduct was consistent with the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients were tapered off psychotropic medications prior to a 3- to 7-day, single-blind, placebo run-in period. Patients who continued to meet entry criteria were randomized in each study to receive either specific fixed doses of lurasidone (range, 40–160 mg/d) or placebo once daily for 6 weeks. Study medication was taken in the morning with food in Studies 1–4 and in the evening with food in Study 5. All patients were initially hospitalized for a minimum of 3–4 weeks of treatment; hospital discharge was then permitted for patients who had achieved a CGI-S score of ≤ 3 or lower and were judged by the investigator to be suitable for outpatient treatment.[3]

The PANSS was administered at baseline (prior to the first dose of study medication) and at weekly visits thereafter through Week 6. For this analysis, the PANSS symptoms were grouped into five factors (positive symptoms, negative symptoms, disorganized thought, hostility/excitement, and depression/anxiety), based on a previously established model [37].

2.3. Statistical methods

Individual patient data from the five studies were pooled for each dose of lurasidone (40 mg/d, 80 mg/d, 120 mg/d, and 160 mg/d) or placebo. The analysis population was the intent-to-treat (ITT) population, which was defined as randomized patients who received at least one dose of study medication and had both a baseline and at least one post-baseline efficacy assessment. Change from baseline for PANSS total and factor scores were determined for each scheduled assessment for all lurasidone doses pooled and for each individual lurasidone dose compared with placebo. Mixed-model repeated measures (MMRM) analyses of change from baseline score were conducted with fixed effects for study, pooled center within study, visit (as a categorical variable), baseline score, treatment, and treatment-by-visit interaction, assuming an unstructured covariance matrix. The *P* values for pairwise comparisons with placebo were not adjusted for multiple comparisons. The effect size for each dose of lurasidone was calculated as the least-squares (LS) mean difference from placebo divided by the pooled standard deviation.

A pattern mixture model analysis using a placebo-based multiple imputation method to account for drop out was performed as a sensitivity analysis of the MMRM results. The results of this analysis were similar to the MMRM results; therefore, it is reasonable to conclude that the MMRM results are robust. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

3. Results

The ITT population from the five studies included 1532 patients who received either lurasidone or placebo. Baseline demographic and clinical characteristics, including illness severity, were similar across the 5 studies, supporting the use of pooled patient data for the purposes of this analysis. For the pooled ITT sample, baseline characteristics were similar for patients treated with lurasidone ($n = 1035$, dose groups pooled) and patients who received placebo ($n = 497$) (Table 1). The majority of patients were male (73.0%),

[2] Study 1 and Study 2 entry requirements included a BPRS score ≥ 42 instead of the PANSS total score ≥ 80 criterion, and a score ≥ 4 (moderate) on two of the seven PANSS positive symptom subscale items without specifying particular items.

[3] Study 2 permitted hospital discharge at the end of Week 4 for all patients, unless the investigator decided that continued hospitalization was clinically indicated.