# Lurasidone Dose Response in Bipolar Depression: A Population Dose-response Analysis

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## ABSTRACT

**Purpose:** Characterization of dose-response relationships for psychotropic agents may be difficult to determine based on results of individual clinical studies, particularly those with a flexible dose design. The goal of this pharmacometric analysis was to characterize the dose-response profile for lurasidone in patients with bipolar depression.

**Methods:** The statistical modeling and simulation analyses reported here were derived from 2 randomized, 6-week, double-blind, placebo-controlled, flexible-dose studies (20–60 mg/d or 80–120 mg/d of lurasidone as monotherapy or 20–120 mg/d adjunct to lithium or valproate) in patients with bipolar depression. Pooled data included 5245 Montgomery-Åsberg Depression Rating Scale (MADRS) observations from 825 patients who had received lurasidone or placebo treatments, with or without lithium or valproate background medication.

**Findings:** The time course of placebo effect on the MADRS score was adequately described by an exponential asymptotic placebo model. A linear dose-response model best described the effect of lurasidone. The net improvement in MADRS score due to lurasidone treatment (the drug effect) was significant ($P < 0.001$), and a positive dose response was detected. Net drug effect after 6 weeks of treatment was estimated to be a 6.0-point decrease in MADRS score per 100 mg of lurasidone. Covariate effects (for age and lithium or valproate use) were significant only for placebo effect parameters; thus, no dose adjustment was necessary related to demographic covariates.

**Implications:** This population dose-response modeling analysis indicates that higher doses of lurasidone are likely to produce greater therapeutic effects in patients with bipolar depression. The linear dose response was consistent for both lurasidone monotherapy and adjunctive therapy in patients with bipolar depression. ClinicalTrials.gov identifiers: NCT00868452, NCT00868699. (*Clin Ther.* 2016;38:4–15) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

**Key words:** atypical antipsychotic, bipolar disorder, depression, dose response, lurasidone, statistical model.

## INTRODUCTION

Bipolar disorder is a serious psychiatric illness characterized by recurring periods of mania, hypomania, and depression.[1] Depressive symptoms dominate the course of the illness[2–4] and are associated with significant impairment in patients' social and occupational functioning[5–8] and an increased risk of suicide.[9,10]

Lurasidone, an atypical antipsychotic agent, is approved for the treatment of schizophrenia in the United States and several other countries and as monotherapy or adjunctive therapy with lithium or valproate for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) in the United States and Canada. Lurasidone possesses high affinity for dopamine $D_2$, 5-hydroxytryptamine $(5\text{-HT})_{2A}$, and $5\text{-HT}_7$ receptors (as an antagonist), moderate affinity for $5\text{-HT}_{1A}$ receptors (as a partial agonist), and no appreciable affinity for $\text{histamine}_1$ or $\text{muscarinic}_1$ receptors.[11] The efficacy of lurasidone in the treatment of patients with

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bipolar depression was revealed in 2 phase III, 6-week, randomized, double-blind, placebo-controlled studies.[12,13] The first study used 2 fixed-flexible dose ranges of lurasidone monotherapy (20–60 mg/d or 80–120 mg/d) compared with placebo.[12] The second study evaluated flexibly dosed lurasidone (20–120 mg/d) compared with placebo as adjunctive treatment with either lithium or valproate.[13]

Dose-response relationships for psychotropic agents may be difficult to determine based on results of individual clinical studies due to various confounds, such as study design, variability in attrition, background medications, and placebo response rates.[14,15] Study designs that use flexible dosing, in which doses are adjusted based on individual response and tolerability, are reflective of usual clinical practice. However, a key limitation of the flexible-dose design is the introduction of selection bias because dose assignment is not random.[16] Therefore, in studies with flexible dosing, it is difficult to associate treatment response with a specific medication dose.

One way to assess and characterize a dose-response relationship from flexible-dose studies is to use pharmacokinetic-pharmacodynamic modeling to link drug exposure to clinical efficacy. A population exposure-efficacy response model allows for separation of the effect of time from the overall effect in flexible-dose studies and provides a longitudinal representation of the treatment effect contributed by placebo, background medication, and study medication. Modeling and study simulation have been used to characterize the association between drug exposure and efficacy in studies of antipsychotic therapy for schizophrenia.[15,17–20]

The goal of the present analysis was to characterize the dose-response profile of lurasidone in the treatment of patients with bipolar depression to inform clinical dosing decisions and identify patient subgroups that might benefit from dose adjustments. Using data from registration studies of lurasidone in patients with bipolar depression, a population exposure-response model was developed to characterize Montgomery-Åsberg Depression Rating Scale (MADRS)[21] score change over time as a function of lurasidone dose. The MADRS is a 10-item, clinician-rated scale; each item is scored from 0 to 6, and item scores are summed to obtain an overall score (range, 0–60).[21] A MADRS score of $\geq$20 indicates depression of moderate or greater severity.[22] A dropout model was also developed to investigate factors affecting attrition patterns and to aid in evaluation of the exposure-efficacy response model. These models were then used to simulate results from a randomized, 6-week, double-blind, placebo-controlled, fixed-dose study.

## PATIENTS AND METHODS

### Study Design and Patients

Data were pooled from the 2 pivotal studies of lurasidone in patients with bipolar depression (study D1050235 [ClinicalTrials.gov identifier: NCT00868452] and study D1050236 [ClinicalTrials.gov identifier: NCT00868699]).[12,13] The monotherapy study (D1050236) evaluated fixed flexible dose ranges of 20–60 mg/d or 80–120 mg/d of lurasidone compared with placebo.[12] The adjunctive study (D1050235) evaluated lurasidone flexible doses between 20 and 120 mg/d compared with placebo as adjunctive treatment with either lithium or valproate.[13] Study procedures were approved by institutional review boards or ethics committees at each study site. Studies were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and with the ethical principles of the Declaration of Helsinki; all patients provided written informed consent before study enrollment.

Study methods are described in detail elsewhere[12,13] and are summarized briefly here. Both studies enrolled adult outpatients, 18 to 75 years of age, who were diagnosed as having bipolar I disorder and experiencing a major depressive episode (defined using *Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition, Text Revision] criteria) with or without rapid cycling and without psychotic features. To be eligible for enrollment, patients were required to have a MADRS score $\geq$20 and a Young Mania Rating Scale score $\leq$12. Key exclusion criteria were a $\geq$25% decrease in MADRS score between screening and baseline, a score $\geq$4 on MADRS item 10 (suicidal thoughts) at screening or baseline, imminent risk of suicide or injury to self or others, an acute or unstable medical condition, lack of response to a $\geq$6-week trial of $\geq$3 antidepressants with or without mood stabilizers during the current depressive episode, and a history of alcohol or substance abuse (previous 2 months) or dependence (previous 12 months).