THE DILEMMA OF LURASIDONE DOSING: A CASE SERIES

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BACKGROUND

Atypical antipsychotics are widely used in the treatment of bipolar disorder.¹ Lurasidone is one of the medications approved by the Food and Drug Administration for the treatment of bipolar depression, both as adjunct and monotherapy.² Similar to other medications in its class, lurasidone has been reported to induce mania in patients being treated for bipolar depression.^{3,4} We present a case series of 4 patients that developed acute mania with lurasidone, an effect that appears to be dose-dependent.

METHODS

We gathered information by direct consultation of the patients and review of the patient charts. Formal consent for presentation was not obtained, hence the data was de-identified. Literature from PubMed and Google Scholar databases was reviewed using a combination of keywords bipolar depression, lurasidone, mania, and atypical antipsychotics.

CASE PRESENTATIONS

- Case A is 16 years old female who was started on lurasidone 20 mg once daily. Two days after starting the dose she had hypersexual behavior, euphoric mood, agitation and decreased need for sleep. Her symptoms subsided over a period of 4 days after the lurasidone was discontinued.
- Case B is a 23-year-old woman with a history of bipolar I disorder who presented to her outpatient with a 1-month history of depressed mood, anhedonia, lack of energy and poor sleep. Lurasidone 40 mg daily was initiated to target bipolar depression. After 7 days of outpatient treatment, she presented to clinic with dysphoric mood, psychotic agitation, and pressure of speech. She wanted to stop lurasidone as she did not like the way it made her feel.
- Case C is a 60-year-old woman with a history of schizoaffective disorder, bipolar type who presented to the outpatient clinic with increased agitation, labile mood, increased activity and racing thoughts after reducing her dose of lurasidone from 80 mg to 40 mg. She had complete symptom resolution after her dose was increased back to 80 mg.
- Case D is a 15-year-old female with diagnosis of bipolar 1 disorder and eating disorder who was well maintained on 60 mg of lurasidone per day. She became symptomatic with her eating disorder and reduced her caloric intake. Within 2 days after reduce caloric intake she presented with grandiosity, euphoric mood, flights of ideas and disinhibited behavior. After restoring her caloric intake and continuing her lurasidone at 60 mg her behavior improved.

Log of Ki values (nM)[†]

HIGH AFFINITY		MODERATE AFFINITY		LITTLE OR NO AFFINITY
Dopamine D ₂	Antagonist	Adrenergic α _{2C}	Antagonist	Muscarinic M ₁ IC ₅₀ >1000 nM
Serotonin 5HT _{2A}	Antagonist	Serotonin 5HT _{1A}	Partial agonist	Histamine H ₁ IC ₅₀ >1000 nM
Serotonin 5HT ₇	Antagonist	Adrenergic α _{2A}	Antagonist	

• The correlation between receptor-binding affinities and clinical outcomes is uncertain

[†]Although the mechanism of action of LATUDA is unknown, the efficacy of LATUDA in bipolar depression could be mediated through a combination of central dopamine Type 2 (D₂) and serotonin Type 2 (5HT_{2A}) receptor antagonism.¹

[†]IC₅₀ = half maximal inhibitory concentration.
The lower the Ki value, the higher the binding affinity.

Receptor binding profile of lurasidone⁸

DISCUSSION

Lurasidone is a drug in the benzisothiazole class approved by the US Food and Drug Administration in June 2013 for the acute treatment of bipolar depression. Lurasidone is a full antagonist at 5-HT_{2A} and 5-HT₇ receptors and partial agonist at 5-HT_{1A} receptor, which may increase dopamine and norepinephrine in the prefrontal cortex. This appears to be the mechanism behind its antidepressant effects.^{2,5} The chemical cascades of similar receptor activity from other atypical antipsychotics have been implicated to induce acute mania.⁶ Despite its full D₂ receptor antagonist properties, lurasidone doses less than 40 mg do not appear to exert antipsychotic effects.⁵ The bioavailability is also highly affected by caloric intake.⁷ The onset of acute mania in our 4 cases appeared to be in response to initiation, dose changes, or fluctuations in bioavailability of lurasidone.

CONCLUSIONS

Our reported cases and the discussed pharmacokinetics and pharmacodynamics of lurasidone, lead to the hypothesis that the efficacy of lurasidone in the treatment of bipolar depression appears to be dose-dependent. Further research is needed to address this dosing dilemma and formulate dosing protocols. Patients should be closely monitored when being treated with lurasidone to prevent substance/medication induced mania.

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