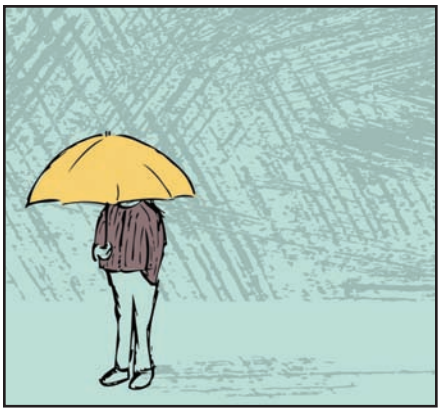

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[REVIEW]

Lurasidone: A New Treatment Option for Bipolar Depression—A Review

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ABSTRACT

Depressive episodes in bipolar disorder contribute to significant morbidity and mortality. Until recently, only quetiapine and an olanzapine-fluoxetine combination were approved to treat bipolar depression. Recently, lurasidone was approved to treat bipolar depression either as monotherapy or adjunctively with lithium or valproate. Lurasidone was well-tolerated, and commonly observed adverse reactions (incidence ≥5% and at least twice the rate for placebo) were akathisia, extrapyramidal symptoms, and somnolence. There were no significant metabolic or electrocardiogram abnormalities. It is taken with food to ensure maximal absorption, and dose should be adjusted in patients who receive moderate CYP450 inhibitors or inducers and in patients with renal disease.

INTRODUCTION

Bipolar depression occurs in approximately one percent of the world population and is defined as a major depressive episode in patients who have experienced at least one episode of mania or hypomania.[1,2] In most patients with bipolar disorder, depressive episodes predominate in frequency and severity; consequently, many patients initially seek treatment for depression.[2] Comorbid psychiatric conditions and metabolic abnormalities result in morbidity and mortality.[3–5] Bipolar depression remains a treatment challenge, with remission rates of only 25 to 60 percent after recommended treatment.[6] Until recently, only quetiapine and an olanzapine-fluoxetine combination were approved to treat bipolar depression.[7,8] In June 2013, the United States Food and Drug Administration (FDA) approved lurasidone to treat bipolar depression, either as monotherapy or adjunctively with lithium or valproate.[7,9,10]

First approved in October 2010 for the treatment of schizophrenia in adults, lurasidone is a benzisothiazol-derivative, second-generation (atypical) antipsychotic. Similar to other atypical antipsychotics, it antagonizes dopamine D_2 receptors, but also serotonin 5-HT_{2A} and 5-HT_7 receptors.[11,12] It is a partial agonist at 5-HT_{1A} receptors. In addition, it antagonizes adrenergic $alpha_{2A}$ and $alpha_{2C}$ receptors but exhibits minimal affinity for histaminic (H_1) and acetylcholinergic muscarinic (M_1) receptors.[11–13] Modulation of serotonin, norepinephrine, and dopamine is the cornerstone of antidepressant pharmacotherapy.[14–17]

Lurasidone may exert antidepressant effects by increasing dopamine activity in the prefrontal cortex through activity at 5-HT_{2A} and 5-HT_{1A} receptors.[14,18] It may enhance serotonin activity by downregulating 5-HT_{2A} receptors.[14,19] In addition, it may increase norepinephrine by antagonizing $alpha_1$ receptors.[10,14,20] Antagonism of 5-HT_7 receptors may improve mood.[9,13,14,18]

EFFICACY

A double-blind, randomized, placebo-controlled trial evaluated the efficacy of lurasidone monotherapy.[21] A total of 505 patients with bipolar depression received lurasidone 20 to 60mg/day, 80 to 120mg/day, or placebo. They were assessed for six weeks using the Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression-Bipolar Version-Severity of illness (CGI-BP-S) scale.[22,23] Individuals receiving lurasidone exhibited significant decreases in MADRS and CGI-BP-S scores compared to those receiving placebo, and progressive improvement was seen starting in the second week.[21]

A double-blind, randomized, placebo-controlled trial evaluated lurasidone's efficacy as adjunctive therapy with lithium or valproate. Already receiving lithium or valproate, 348 patients with bipolar depression received lurasidone 20 to 120mg/day or placebo. They were assessed for six weeks using the MADRS and CGI-BP-S. Starting in the third week, the treatment group reported greater symptom improvement compared to the placebo group.[24] A *post-hoc* analysis using the metrics of numbers needed to treat and numbers needed to harm evaluated both studies' data and concluded that lurasidone yielded comparable benefits and less risk of harm compared to quetiapine and olanzapine-fluoxetine.[25]

TOLERABILITY

Lurasidone was well-tolerated in both trials.[21,22] In the monotherapy study, discontinuation rates for both groups were similar. Common side effects were nausea, akathisia, extrapyramidal symptoms, sedation, and vomiting. Headache was most prominent in patients receiving lower doses (20–60mg/day).[21] Metabolic changes with lurasidone were minimal and no QTc interval prolongation was reported. As adjunctive therapy, the discontinuation rate for lurasidone was six percent compared to eight percent for placebo. Adverse effects included nausea, extrapyramidal symptoms, somnolence, tremors, akathisia, and insomnia. It caused minimal changes in the metabolic profile and insignificant prolongation of the QTc interval.[24]

DOSING

Lurasidone is available in 20, 40, 60, 80 and 120mg tablets given once daily with food (at least 350 calories) to ensure maximal absorption, and the starting dose is 20mg/day with titration up to 120mg/day[11] For individuals receiving moderate CYP3A4 inhibitors, clinicians should start with 20mg/day (or reduce lurasidone to half of the original dose) and not exceed 80mg/day. For patients receiving moderate CYP3A4 inducers, the lurasidone dose may be increased after one week as clinically indicated. The recommended starting dose for patients with moderate and severe renal impairment is 20mg/day, not to exceed 80mg/day. The recommended starting dose for patients with moderate and severe hepatic impairment is 20mg/day, not to exceed 40mg/day in severe and 80mg/day in moderate impairment. No dose adjustment is required when given with lithium or valproate.

Following oral administration, lurasidone is quickly absorbed and reaches maximum plasma concentration (T_{max}) in 1 to 3 hours and steady state within one week.[11] Its bioavailability is 9 to 19 percent and can be increased by food intake.[11,18] Lurasidone primarily undergoes hepatic metabolism by the CYP450 3A4 isozyme.[6,11] Strong inhibitors of CYP3A4 (e.g., ketoconazole) increase plasma levels sevenfold, whereas moderate inhibitors (e.g., diltiazem) increase plasma concentration by twofold.[11] Conversely, strong CYP3A4 inducers (e.g, rifampin) decrease lurasidone concentrations by 85 percent.[6] No significant interactions have been demonstrated when lurasidone is given with lithium, oral contraceptives, or midazolam.[11,18] It is eliminated primarily in feces and the remainder in urine.[11]

CONTRAINDICATIONS

Lurasidone is contraindicated in patients who are hypersensitive to lurasidone or any formulation components, or who are receiving strong CYP3A4 inducers or inhibitors.[11,18] As with other antipsychotics, lurasidone carries the risk of seizure, tardive dyskinesia, hyperprolactinemia, metabolic abnormalities, and a "black box" warning for increased mortality in elderly patients with dementia-related psychosis.[11] Due to its serotonergic antidepressant effect, there is a warning for risk of mania (in patients with bipolar disorder) and suicidal thinking/behavior (in children, adolescents, and young adults). As a Category B drug, it should be used during pregnancy only if the potential benefit justifies potential risk to the fetus.[11] After weighing the risks of drug discontinuation and potential symptom exacerbation with their clinicians, nursing mothers are recommended to discontinue either the drug or nursing.[11] Due to adrenergic receptor activity, patients should be aware of the risk for orthostatic hypotension.

CONCLUSION

Bipolar depression is a debilitating condition and contributes to morbidity and mortality. Treatment options are limited, and quetiapine and olanzapine-fluoxetine have demonstrated efficacy but possess significant metabolic risks. Lurasidone has demonstrated effectiveness in treating bipolar

depression with minimal adverse effects and a low metabolic risk profile.[7,18] Its low affinity for acetylcholine and histamine receptors produces minimal risk of cognitive deficits and weight gain.[12,13] Although these studies were of short duration, evaluated efficacy for patients with bipolar disorder I, and did not establish efficacy as maintenance therapy, lurasidone appears to be a metabolically favorable, well-tolerated treatment option for clinicians who treat patients with bipolar depression.

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