Lurasidone
A new atypical antipsychotic

NICHOLAS KEKS MB BS, MPM, PhD, FRANZCP
JUDY HOPE MB BS(Hons), MPM, PhD, FRANZCP

Lurasidone is a new atypical antipsychotic that is effective for short- and long-term treatment of patients with schizophrenia. It joins ziprasidone and aripiprazole as 'metabolically friendly' treatments but, unlike ziprasidone, has a low risk of causing QT prolongation. Possible side effects include akathisia and parkinsonism.

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Schizophrenia and related psychotic disorders share the common aetiology of brain dopamine dysregulation. Midbrain dopamine overactivity is hypothesised to cause delusions, hallucinations and formal thought disorder. All antipsychotics block dopamine D_2 receptors to some extent and remain the cornerstone of treatment for patients with psychoses. The new generation or atypical antipsychotics distinguish between the D_2 receptors thought to be responsible for psychosis and those responsible for movement, resulting in a low risk of extrapyramidal side effects such as parkinsonism. However, these drugs can cause other problems, most particularly weight gain and metabolic syndrome.[1]

Apart from amisulpride (a benzamide), all atypical antipsychotics are serotonin-dopamine antagonists (although aripiprazole is a partial antagonist). Clozapine is the prototype drug of the group and remains the most effective medication for patients with treatment-resistant schizophrenia but is associated with agranulocytosis, cardiac effects, convulsions, marked weight gain, diabetes and hyperlipidaemia. Ziprasidone and aripiprazole are 'metabolically friendly' antipsychotics (with a low risk of weight gain) that have been available for some time but are not as effective as clozapine and some other atypical antipsychotics.[2]

Lurasidone is another metabolically friendly antipsychotic. Developed in Japan and first released in 2013, lurasidone has now been approved by the TGA for treatment of schizophrenia in adults and is listed on the PBS. At issue is whether lurasidone is a useful new option for the treatment of psychoses, given the wide variety of drugs already available.

What is lurasidone?

Lurasidone is a serotonin-dopamine antagonist antipsychotic that blocks the D_2 receptor as well as 5-hydroxytryptamine (serotonin, 5-HT) receptor subtypes 5-HT_2 and 5-HT_7. It is also a partial agonist at the 5-HT_{1A} receptor but an antagonist at noradrenergic α receptors. It has no significant antihistaminic or anticholinergic activity. The drug is rapidly absorbed if taken with food and has a mean half-life of about 18 hours, so that it is taken once a day, and reaches steady state within seven days. Lurasidone is metabolised in the liver mainly by cytochrome P450 3A4 (CYP3A4); there is also some renal excretion.[3]

Is lurasidone effective?

In short-term studies, lurasidone demonstrated effectiveness in treating acute schizophrenia compared with placebo. In longer term (12-month) studies, lurasidone demonstrated efficacy against relapse of schizophrenia equivalent to quetiapine, but a study comparing lurasidone with risperidone could not demonstrate equivalent efficacy.[4,5] An authoritative meta-analysis reported that the antipsychotic efficacy of lurasidone is less than that of drugs such as olanzapine and risperidone, which in turn are less

MedicineToday 2016; 17(9): 56-57

Professor Keks is Professor of Psychiatry at Monash University; and Director of the Centre for Mental Health Education and Research at Delmont Private Hospital, Melbourne, Vic. Dr Hope is Senior Lecturer at Monash University; Deputy Director of the Centre for Mental Health Education and Research at Delmont Private Hospital; and a Consultant at Eastern Health, Melbourne, Vic.

effective than clozapine.[2] Lurasidone is broadly in the same category for antipsychotic efficacy as quetiapine, ziprasidone, aripiprazole and asenapine.[2]

Another possible therapeutic use for lurasidone emerged when two studies demonstrated that the drug has antidepressant properties in patients with bipolar depression, when used as monotherapy or in combination with lithium or valproate.[6,7] Bipolar depression is a common cause of treatment-resistant depression, leading to chronic suffering and suicide risk. Lurasidone was approved for treatment of bipolar depression by the US Food and Drug Administration in 2013. Lurasidone is not approved for treatment of bipolar depression in Australia.

What are the side effects?

Probably the main concern with lurasidone is that in early treatment it can cause akathisia (restless legs syndrome, an extrapyramidal side effect), which can lead to torment and agitation. Parkinsonism can develop with longer-term use. Some patients report somnolence; postural hypotension can occur. On the other hand, the risk of weight gain and consequent metabolic syndrome is low (equivalent to that with ziprasidone).[2,3] The risk of QT prolongation is lower than with any other antipsychotic. The risk of prolactin elevation is low.[2,3]

How should lurasidone be given?

Lurasidone is available as 40 and 80 mg tablets. Patients should be started on 40 mg taken at night, and the dose must be taken with a significant amount of food to ensure adequate absorption. Most patients are likely to need either 40 or 80 mg of lurasidone daily. The maximum recommended dose is 160 mg daily, but few patients benefit from high doses and most of the side effects are dose dependent. No dose adjustment appears to be needed in older patients. Hepatic and renal impairment increase blood concentrations of the drug.[3]

Are there significant drug interactions?

Few drugs interact with lurasidone; however, blood concentrations of the drug are reduced by CYP3A4 inducers such as carbamazepine and St John's wort. Patients should avoid grapefruit juice, which increases blood concentrations of the drug.[3]

Conclusion

As a treatment for patients with schizophrenia, lurasidone joins ziprasidone and aripiprazole as an atypical antipsychotic that is metabolically friendly (low risk of weight gain) and also unlikely to cause significant hyperprolactinaemia. In contrast to ziprasidone, lurasidone has a low risk of causing QT prolongation. The side effects of akathisia early in treatment and parkinsonism with longer-term treatment may be a significant challenge with the drug. Some practice points on lurasidone are summarised in the Box.

A major feature of lurasidone is its possible antidepressant efficacy in patients with bipolar depression. As bipolar depression is often highly treatment resistant, the prospect of a new effective treatment is welcome. However, more research is needed to explore the role of the drug in bipolar disorder, and lurasidone is not approved for the treatment of patients with bipolar depression in Australia. MT

PRACTICE POINTS

- Lurasidone is a new serotonin-dopamine antagonist atypical antipsychotic.
- It is effective for the short- and long-term treatment of patients with schizophrenia and is approved for this indication in Australia and listed on the PBS.
- It may also act as an antidepressant in patients with bipolar depression, but is not approved for this indication in Australia.
- Lurasidone is associated with a low risk of weight gain and metabolic syndrome, on par with ziprasidone and less than the risk with other atypical antipsychotics.
- Lurasidone is associated with a low risk of QT prolongation and also of hyperprolactinaemia.
- Side effects of lurasidone include akathisia, parkinsonism and somnolence.
- Lurasidone can be considered as an option for antipsychotic treatment of patients in whom weight gain and hyperprolactinaemia are not acceptable.

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COMPETING INTERESTS: None.