New Treatment Paradigms in Bipolar Depression: *Symposium Highlights*

The diagnosis and management of bipolar depression remain challenging. Lurasidone, a relatively new second-generation antipsychotic (SGA), has been recommended by international guidelines as a first-line treatment regimen in adults and adolescents with bipolar depression.[1,2] At a symposium organised by the Asian Association of Neuropsychopharmacology (AANP) and the Society for Advancement of Bipolar Affective Disorder on 13th January 2023, three experts were invited to share the clinical evidence and experience using lurasidone for the treatment of bipolar depression.

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Setting New Treatment Paradigms in the Management of Bipolar Depression

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Treatment of bipolar depression in adult patients

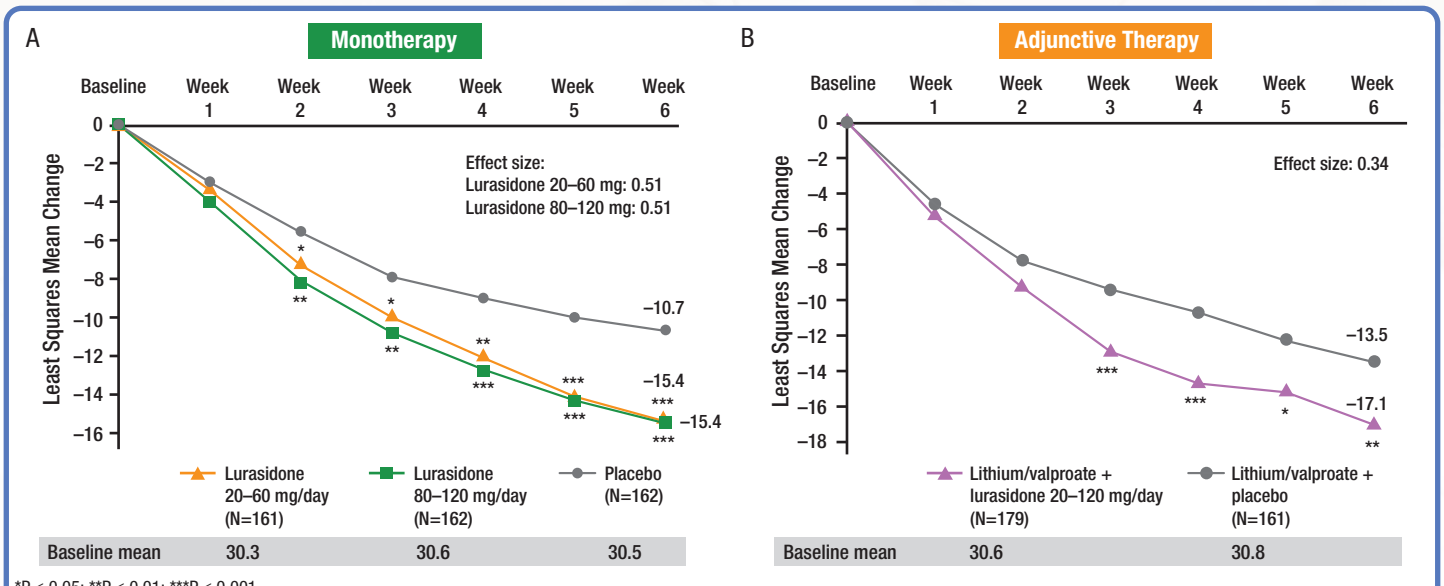
Two randomised placebo-controlled trials and a subsequent open-label extension study demonstrated that, in adult patients with bipolar depression, lurasidone, as monotherapy or adjunctive treatment, was associated with significant reductions in the primary endpoints, scores on the Montgomery–Àtreat Depression Scale (MADRS; Figure 1), and significant improvements in various secondary endpoints, including depression severity scores, anxiety symptoms, and patient-reported measures of quality of life (QoL) and functional impairment.[3–5] The safety profile of lurasidone was tolerable, with minimal changes in bodyweight or metabolic parameters.[3–5]

Treatment of bipolar depression in children and adolescents*

Lurasidone is also effective and well tolerated for the treatment of bipolar depression in paediatric patients.[6] In a randomised placebo-controlled trial of patients aged 10–17 years (N = 347), lurasidone monotherapy (20–80 mg/day) significantly reduced depressive symptoms in terms of the Children's Depression Rating Scale–Revised total scores, and improved depression severity scores, anxiety, QoL and global functioning, with minimal effects on bodyweight and metabolic parameters.[6] The Royal Australian and New Zealand College of Psychiatrists (RANZCP) have recommended that children and adolescents with bipolar depression may be managed with psychosocial treatments in conjunction with lurasidone monotherapy or a combination of an SGA and an antidepressant.[2]

Controversy regarding the role of antidepressants in bipolar disorder

Although the prescription rate of antidepressants is high in bipolar depression,[7,8] there is a growing body of clinical trial data that casts doubt on their clinical utility.[9–12] A meta-analysis of 15 randomised trials demonstrated that antidepressants (primarily as adjunctive therapy) were not statistically superior to placebo or other current standard treatment for bipolar depression (P = 0.06).[13] Most negative studies of antidepressants for bipolar depression to date used paroxetine.[12,14,15] According to the RANZCP, antidepressant monotherapy should be



*P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001.

Figure 1. *Least squares mean changes in MADRS among patients treated with lurasidone alone (A) or in addition to lithium/valproate (B) versus placebo.[3,4]*

*In Taiwan and Thailand, lurasidone was approved for monotherapy for the treatment of child and adolescent patients (10 to 17 years) with major depressive episodes associated with bipolar I disorder. In Hong Kong, Singapore, and Malaysia, lurasidone was approved for monotherapy for the treatment of adolescent patients (13 to 17 years) with major depressive episodes associated with bipolar I disorder.

avoided in bipolar disorder, whereas adjunctive antidepressant therapy should be used cautiously in the treatment of bipolar depression when there is a history of antidepressant-induced mania, current or predominant mixed features, or a history of rapid cycling.[2]

Summary

Lurasidone is an SGA, used as either monotherapy or adjunctive therapy, that offers significant improvements across various symptom profiles and functional and QoL measures, with a favourable safety profile (Table 1)[16–18] among adult and adolescent populations with bipolar depression.[3,4,6] Lurasidone goes beyond efficacy to help patients achieve wellness and good QoL. The **Canadian Network for Mood and Anxiety Treatments** and the **International Society for Bipolar Disorders** have recommended **lurasidone as one of the first-line treatment regimens for bipolar depression**.[1]

Table 1. Safety of atypical antipsychotics in bipolar disorder based on the speaker's opinions.

Drug	Risk of weight gain	Risk of other metabolic events	Risk of EPS	Risk of increased prolactin	Risk of ECG alteration
Aripiprazole					
Asenapine					
Lurasidone					
Olanzapine					
Paliperidone					
Quetiapine					
Risperidone					
Ziprasidone					

Green = No difference from placebo; yellow = higher risk than placebo; red = higher risk than placebo and an active comparator.
ECG = electrocardiogram; EPS = extrapyramidal symptoms.

Considerations for Using Lurasidone in Bipolar Depression (Case Sharing)

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Background

The patient was a 34-year-old woman who earned a Master of Business Administration and served as a manager in a multinational company. She had a good relationship with her boyfriend.

Case presentation

October 2016 (aged 29)

- Depressive episodes associated with bipolar I disorder experienced
- Treated with sertraline for 3 months
- No follow-ups with the treating physician

June 2018 (aged 31)

- A manic episode with mixed features
- Consulted Dr. Pariwatcharakul
- Treated with quetiapine 500 mg/day + lamotrigine 300 mg/day

August 2018

- Remission
- Weight gain (possibly due to her obsession with durians during her most recent manic episode and/or quetiapine treatment)

August 2018–January 2019

- Continuation phase
- Quetiapine reduced to 400 mg/day
- Continued lamotrigine 300 mg/day (to ensure control of depressive symptoms, which the patient felt were more troublesome than manic ones)

January–mid-February 2019

- Continued lamotrigine 300 mg/day
- Tapered off quetiapine over 6 weeks to avoid withdrawal symptoms

March 2019 (aged 32)

- Recurrence of depressive symptoms
- **Add-on treatment with lurasidone 20 mg/day** + clonazepam 0.5 mg as-needed (for insomnia)

Mid-March 2019

- Continued lamotrigine 300 mg/day + **lurasidone 40 mg/day**
- Unwilling to receive quetiapine (due to the risk of metabolic side effects) or lithium

Late April 2019

- Continuation phase: lamotrigine 300 mg/day + **lurasidone 30 mg/day**
- Akathisia experienced (mostly on Friday nights; absent before the continuation phase)
- The patient revealed that she often had **high-fat meals** (e.g. hotpot) on Friday nights, which may **increase the absorption of lurasidone** and resemble a dose increment
- Remission

A Case Report of Bipolar Depression from Hong Kong

Dr. Michael Wong
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Chairman of the Hong Kong Chapter of AANP

Background

Mr. Lam, 39, was married and lived with his wife, daughter and a domestic helper. He ran an online shopping business. In his early years, he had studied design and been employed as a designer. Unwilling to help with his family's manufacturing business, he had chosen to find a job in Hong Kong. Despite having a history of Grave's Disease, he had normalised thyroid function after several years of treatment. He had no known history of diabetes mellitus, hypertension or heart disease.

Case presentation

2008

- 1st episode of depression (low mood, loss of motivation/interest, feeling lonely/hopeless)
- No active treatment; recovered after several months

2018–2021

- 2nd episode of depression (low mood [worst in the morning], crying often, reduced enjoyment/motivation, loss of interest in hobbies)
- Had thoughts of giving up on life, but no definite suicidal idea/plan
- Felt stressful/fearful
- Still able to work

June 2022

- Worsened mood after a quarrel with family members (concerning the family business)
- Consulted a private psychiatrist (Dr. X)
- Treatment with lorazepam + trazodone + zopiclone; mood improved

October 2022

- Became happier
- Felt more competent/talkative/motivated/efficient
- Rapid thoughts with many ideas
- Invested money based on intuition/overconfidence, instead of detailed analysis or consultation, resulting in a significant financial loss
- Made many careless mistakes and became irritable, scolding staff when his mistakes were pointed out
- No excessive spending
- Slept well
- No change in appetite or bodyweight
- Felt recovered from depression

November 2022

- Follow-up with Dr. X; treatment with trazodone stopped
- Mood deteriorated
- Felt tired, loss of energy/drive/motivation
- Insomnia
- Poor appetite
- Recurrence of suicidal ideas, but no real attempt

December 2022

- Dr. X stepped up fluoxetine to 60 mg daily, but no improvement
- Felt anxious, with worsened mood
- Self-stoppage of fluoxetine treatment

January 2023

- Consulted Dr. Wong
- **Bipolar depression** was diagnosed
- **Antidepressant treatment stopped**
- Administered **lurasidone 20 mg (in the evening)** as a treatment for bipolar depression, with a low risk of switching to a manic state
- Received treatment with pregabalin for anxiety and zopiclone for insomnia

Follow-up in 1 week

- Slight improvement in mood
- Crying sometimes, but with less negative thoughts
- Participated in exercise (boxing)
- Improvement in sleep
- **Lurasidone stepped up to 40 mg**

Follow-up in 2 weeks

- Improvement in mood (self-rated as "in a neutral position")
- Reduced crying and negative thoughts
- Improvement in concentration, albeit lower than the premorbid level
- No manic symptoms
- Continued treatment with **lurasidone 40 mg**, with **good response and rapid, remarked improvement in depressive symptoms**

Q&A

Q1: Once depressive symptoms are resolved, should we stop adjunctive lurasidone treatment and just keep a mood stabiliser?

Prof. Baune: In my clinical practice, in cases of combination therapy, lurasidone is kept for at least 2 years, because longer-term treatment is necessary to improve functioning and QoL.

Dr. Pariwatcharakul: Lurasidone treatment will be continued. Half of my patients have used the same dose as that used in the acute phase, while another half have used lower doses, e.g. 40–60 mg or even 20 mg for younger patients. In my clinical observation, combination therapy appears to be associated with greater improvement in cognitive symptoms compared with monotherapy with a mood stabiliser. Patients who seek combination therapy are mostly professionals, e.g. doctors.

Dr. Wong: The patient's medical history will be considered. If he/she requires add-on lurasidone because of a suboptimal response to a mood stabiliser, combination therapy should be continued to ensure symptom control using the different mechanisms of action of these drugs.

Note: The main objective (primary endpoint) measured at the end of lurasidone clinical studies was the reduction in bipolar depression symptoms. Another objective in these clinical studies was to measure the impact of lurasidone on QoL as a secondary endpoint. These results should be interpreted with caution as they are observational and descriptive in nature.

Q2: How do you treat pregnant/lactating women with bipolar depression?

Dr. Pariwatcharakul: Most antipsychotics are classified as Pregnancy Category C. For those who are in remission, I will avoid prescribing these medications and put an emphasis on long-term care, e.g. mollifying their stress. If there is a strong clinical need, I will discuss with the patient and family, and consider monotherapy with an antipsychotic that appears to have a lower risk as per the NICE guidelines.[19] However, it is unnecessary to switch medications based on the indirect data used in the guidelines. When truly needed, antipsychotic treatment will just be initiated on the 2nd trimester to avoid the impact on the development of major foetal organs during the 1st trimester. Notably, valproate should be avoided in pregnant/child-bearing women. For lactating women, I will assess the severity of post-pregnancy depression before initiating treatment. In cases of no/mild depression, I will use non-medicinal approaches, such as cognitive behavioural therapy and measures to improve sleep hygiene. Patients should also know how to take care of themselves. For example, they may need another person's help to take care of the baby at night.

Prof. Baune: Valproate and lithium should be avoided in pregnancy. When clinically indicated, some antipsychotics (e.g. quetiapine and lurasidone) and antidepressants (e.g. paroxetine) can be used in pregnant women. However, these medications should be avoided during the 1st trimester and only be used during the 2nd or 3rd trimester. In addition, external/environmental risk factors should be managed. For example, a calm and quiet surrounding is required for good sleep.

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