



Bipolar Optimal Treatment Goal: Achieving Symptom Control and Functional Improvement with LAI

The target of the contemporary management of bipolar disorder is functional recovery, instead of mere symptom improvement or remission.¹ Up to 60% of individuals with bipolar disorder are reported to have functional impairment (defined as the Functioning Assessment Short Test [FAST] total score > 11), which is significantly associated with multiple factors, such as the number of previous manic episodes and treatment nonadherence.^{2,3} At the Society for Advancement of Bipolar Affective Disorder Annual Scientific Meeting 2022, Professor Eduard Vieta from the University of Barcelona, Spain, reviewed the role of long-acting injectable (LAI) antipsychotics, particularly aripiprazole once-monthly (AOM), in the long-term treatment of bipolar disorder. Additionally, Dr. Ki-Yan Mak, an expert in psychiatry practising in Hong Kong, shared a case to illustrate the considerations for choosing AOM.



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Impact of treatment nonadherence

Noncompliance with medication is a common phenomenon and the major cause of recurrence among individuals with

bipolar disorder.⁴ A prospective study of patients with mood disorders treated with mood stabilisers showed that, at 18 months, rates of hospitalisations were significantly higher in partially adherent patients than in fully adherent patients, regardless of therapeutic plasma levels (Figure 1).⁵ The risk of hospitalisations increases with every new episode of relapse among bipolar individuals (Figure 2).⁶ Frequent treatment switching during an acute phase is another issue among patients with bipolar disorder.⁷ Treatment regimens should be optimised to improve adherence in order to reduce the risk of relapse and hospitalisations.

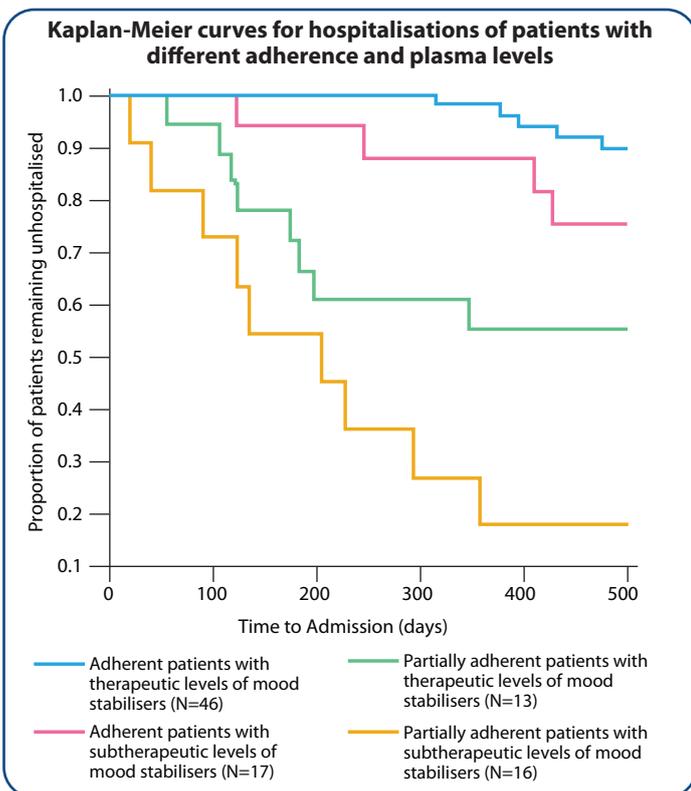


Figure 1. Kaplan-Meier survival curves for hospitalisations of patient groups defined by self-reported adherence to treatment with mood stabilisers and serum plasma levels.⁵

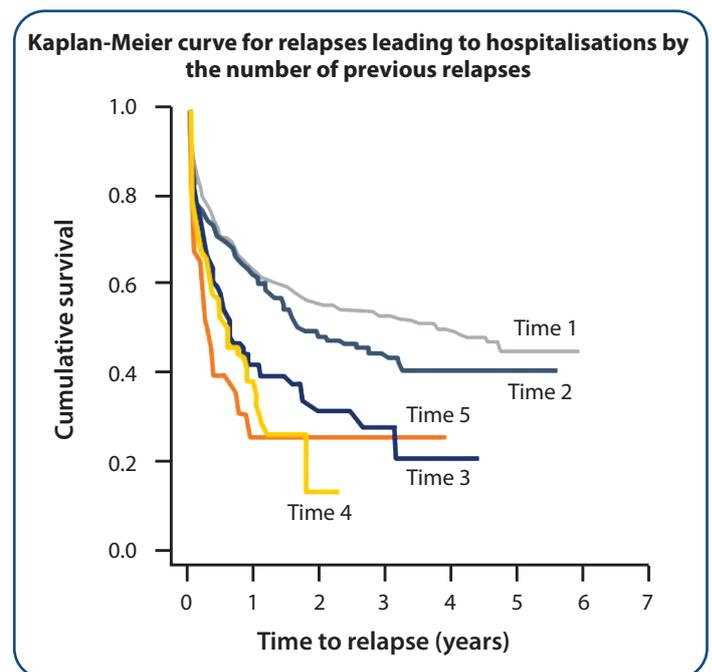


Figure 2. Rate of relapse leading to hospitalisation (after being discharged for ≥ 3 days) following the first, second, third, fourth and fifth discharges for men with bipolar affective disorder.⁶

Role of LAIs

For patients with psychiatric disorders, LAIs facilitate monitoring of treatment adherence, identification of poor response and poor adherence, formation of a therapeutic alliance with healthcare providers through regular follow-up visits, and maintenance of stable therapeutic plasma levels.^{8,9} A Finnish nationwide cohort study of patients with bipolar disorder showed that patients using LAIs were associated with a significantly lower risk of psychiatric re-hospitalisations compared with their oral counterparts (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.55 – 0.90; $P = 0.005$).¹⁰ According to Pacchiarotti et al, bipolar individuals who have good tolerability to the corresponding oral antipsychotics and of at least one of the clinical scenarios listed in Table 1, may consider using LAIs as maintenance treatment to improve adherence and reduce manic recurrences.¹¹

AOM for the maintenance treatment of bipolar disorder

In a randomised trial of bipolar individuals with a manic episode who were stabilised sequentially on oral aripiprazole and AOM,

Individuals at risk of stopping medication on their own, with:

- a **severe, psychotic manic episode**;
- a **history of relapse** after discontinuation of antipsychotic medication;
- **predominantly manic episodes or manic predominant polarity**;
- **partial or no response** to conventional mood stabilisers;
- **schizoaffective disorder, bipolar type**; and
- a **rapid cycling** course.

Table 1. Potential indications for bipolar disorder maintenance treatment with long-acting injectable (LAI) antipsychotics.¹¹

those who continued to receive AOM exhibited a significantly delayed time to recurrence of any mood episode, with 55% reduced risk of recurrence vs. placebo (HR, 0.45; 95% CI, 0.30 – 0.68; $P < 0.0001$; Figure 3A) and had a significantly lower rate of recurrent mood episodes (26.5% vs. 51.1%; $P < 0.0001$; Figure 3B) compared with the placebo group.¹² The two groups had no significant differences in the rate of depressive episodes.¹² AOM was generally well tolerated, with few discontinuations due to treatment-emergent adverse events (17.4% vs. 25.6% for placebo).¹²

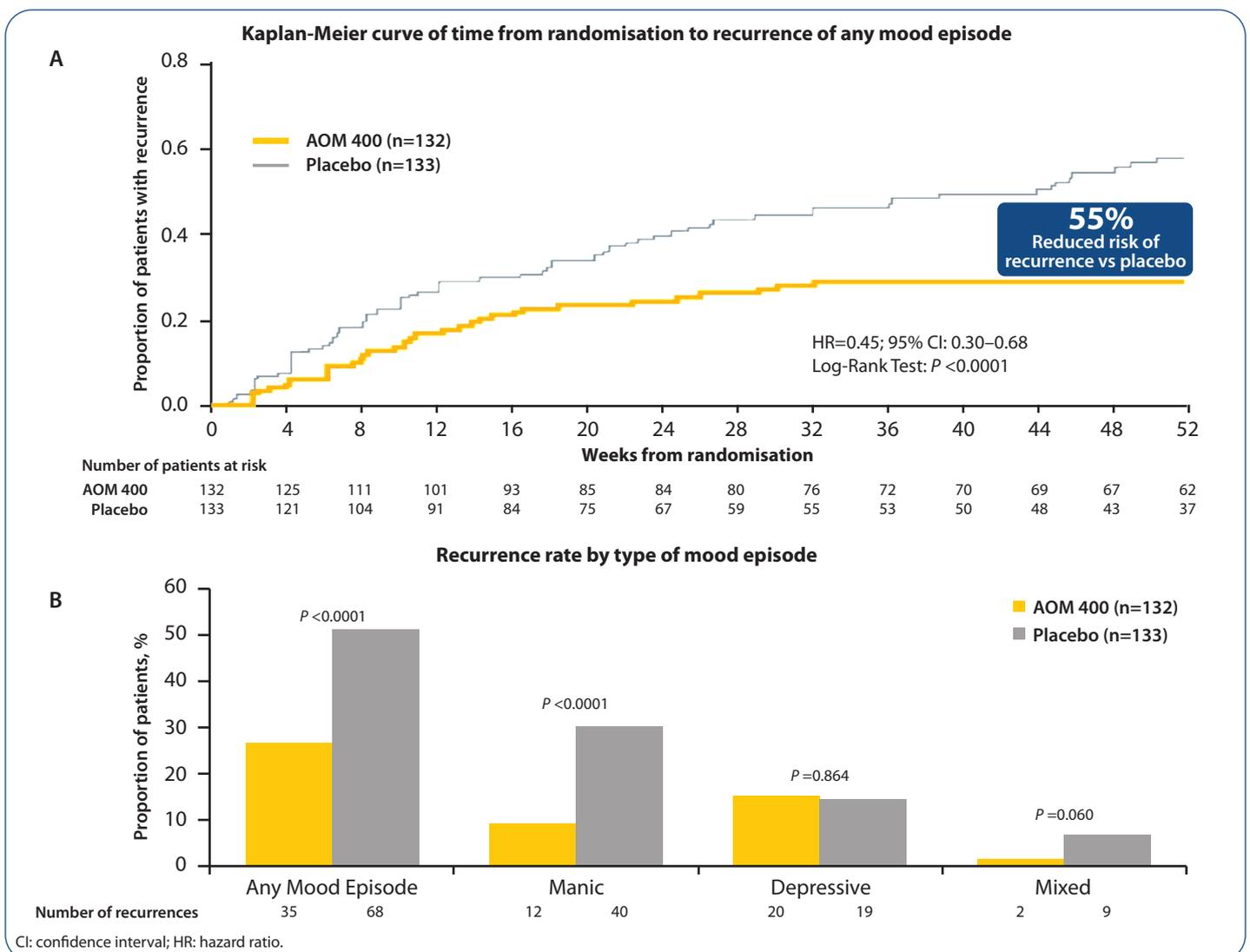


Figure 3. Proportion of patients with recurrence from randomisation to week 52 (A) and recurrence rate by type of mood episode (B) among bipolar individuals who received aripiprazole once-monthly 400 mg (AOM 400) or placebo.¹²

AOM vs. other LAIs

A real-world study of bipolar individuals showed that AOM was associated with significantly lower risks of all-cause and psychiatric hospitalisations compared with LAI formulations of haloperidol and risperidone during 1-year and 3.5-year follow-ups (Figure 4).¹³

Treatment acceptability and functional recovery among patients who received AOM

Maintenance treatment with AOM offers promising long-term outcomes from patient's perspective. In an open-label study of bipolar individuals who were previously exposed to AOM in a randomised trial (rollover) or had newly received AOM right after stabilisation on oral aripiprazole (de novo), > 70% of participants in both groups were extremely or very satisfied with AOM maintenance treatment (Figure 5).¹⁴ A subsequent post hoc analysis showed that de novo participants had significant improvement in functional recovery from baseline

(mean FAST score, 17.90) to the end of the 4- to 12-week stabilisation phase (14.02), which was maintained during the 52-week maintenance phase (13.98).¹⁵

Case sharing

A 36-year-old woman was admitted to hospital for a second episode of acute mania. Two years prior, the first episode had occurred and was treated with oral risperidone and lithium. After 1 year of treatment, risperidone was slowly tapered off, and serum levels of lithium were 0.5 mEq/L. Notably, because the patient frequently forgot to take medications, she became fully manic with psychotic symptoms in 2 weeks, and was subsequently hospitalised. To improve treatment adherence, manic episodes, menstrual problem and weight gain, the patient has been initiated on oral aripiprazole followed by AOM 400 mg on top of lithium. This regimen might be useful to help achieve the balance on maintaining treatment adherence and medication side effects.

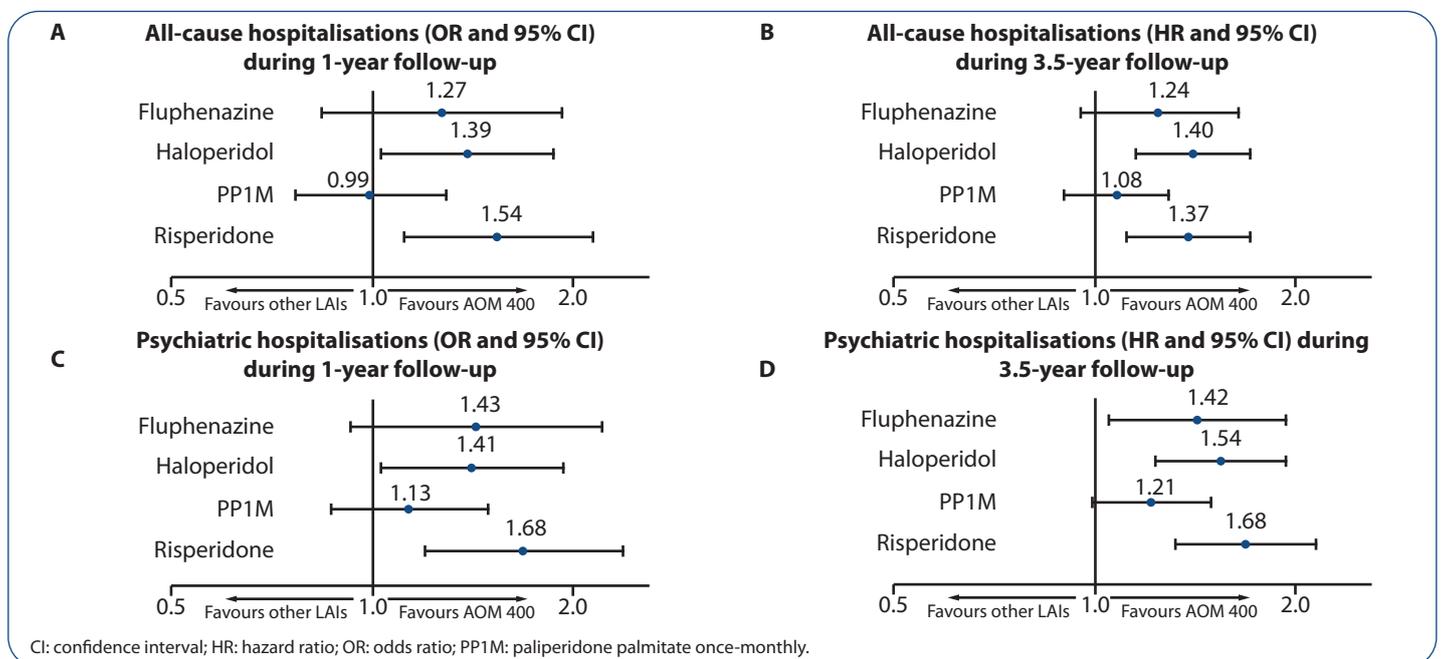


Figure 4. Risk of all-cause hospitalisations (A and B) and psychiatric hospitalisations (C and D) among bipolar patients who received aripiprazole once-monthly 400 mg (AOM 400) or other long-acting injectable (LAI) antipsychotics during 1-year and 3.5-year follow-ups.¹³

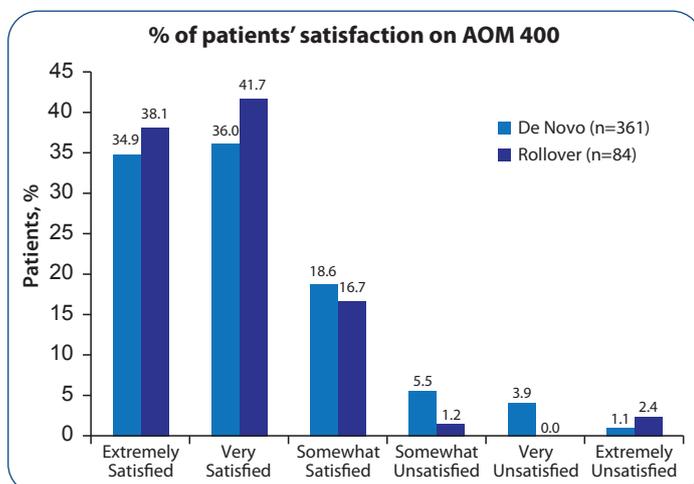


Figure 5. Evaluation of satisfaction with aripiprazole once-monthly 400 mg (AOM 400) as maintenance treatment among bipolar individuals who were previously exposed to AOM 400 in a randomised trial (rollover) or had newly received AOM 400 (de novo).¹⁴

Summary

- **High rates of functional impairment** are reported in individuals with bipolar disorder, and impairment still apparent in euthymia.^{2,3}
- For most bipolar individuals, **each relapse leads to progressive impaired functioning.**^{2,3}
- **LAIs are more effective** than oral antipsychotics in **preventing re-hospitalisations** in bipolar disorder.¹⁰
- **LAI treatment can maintain long-term functional improvement.**¹⁵
- **AOM is an important tool** for the maintenance treatment of bipolar disorder.¹²⁻¹⁵

“Maintained on Maintena” – Local Case Sharing



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Case vignette

Ms. H was a single, 37-year-old professional living with her mother. Referred to Dr. Mak’s clinic by her friend, she was looking for treatment for continuous fluctuation of mood that affected her work, which required dexterity (fine motor skills). Her personality was pessimistic and unsociable. She had been hardworking during school years, with good academic performance, and had no past severe traumatic experiences.

Occupational background

Ms. H was a senior civil servant with over 10 years of experience. Mood fluctuation affected her work performance, leading to absenteeism and presenteeism. She frequently stayed in bed for a whole day and did not care about the consequence of absence from duty, which put her at risk of being laid off and necessitated a medical board to review her mental status. Notably, initiation of LAI treatment improved her conditions, with decreased sick leaves and fewer occasions of being late for work.

Medical history

In 2005, Ms. H had felt depressed for 5 years and sought help from a counsellor. She was worried financially about a mortgage, with worsening symptoms such as lying-in bed all

the time. She felt better after a private psychiatrist prescribed fluoxetine for her; however, 2 years later, she relapsed with depression, tearfulness, and suicidal thoughts, which did not respond well to treatment with mirtazapine for 6 months. She was switched to treatment with venlafaxine and diagnosed with bipolar disorder after a hypomanic (instead of manic) episode. Electroconvulsive therapy was initiated for a recurrence of severe depression and suicidal thoughts.

Other issues

Ms. H experienced fluctuation in body weight, with a history of a 20-lb increase. She had a strong family history of psychiatric disorder, her mother and elder sister had been hospitalised for depression. Past prescriptions for Ms. H included flupentixol/melitracen, bupropion, lithium, topiramate, and thyroxine. Despite having some gynaecological problems such as premenstrual syndrome, she was generally healthy. Notably, her drug compliance became poor in case of low mood.

Treatment history

Figure 6 illustrates the treatment journey of Ms. H. After treatment with oral antipsychotics, benzodiazepines, sodium valproate, and serotonin-norepinephrine reuptake inhibitors, Ms. H was prescribed risperidone LAI for the maintenance treatment of bipolar disorder. However, adverse effects (AEs), including akathisia, sedation, and tremor, affected her work performance, which demanded dexterity and concentration. She was switched to maintenance treatment with AOM, which was associated with no akathisia, fewer post-injection AEs, and insignificant weight gain.

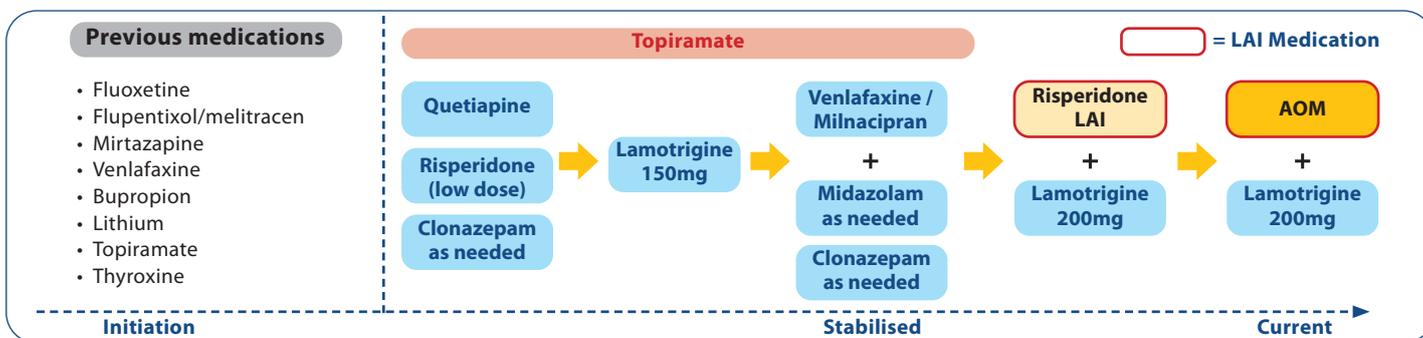


Figure 6. Treatment journey of Ms. H.

| Drug class | Possible long-term AEs affecting females |
|----------------------|--|
| Dopamine antagonists | <ul style="list-style-type: none"> • Hyperprolactinaemia • Affect breastfeeding • Affect pregnancy • Weight gain (affected by the “pines”) |
| Valproate | <ul style="list-style-type: none"> • Amenorrhoea (polycystic ovary syndrome) • Weight gain • Hair loss |
| Mood stabilisers | <ul style="list-style-type: none"> • Teratogenicity (leading to birth defect) |

Table 2. Possible long-term, female-specific adverse effects (AEs) associated with psychiatric medications (based on Dr. Mak’s clinical experience).

Remarks

When treating patients whose jobs require advanced concentration, memory, and motor activity, such as surgeons, dentists, pilots and technicians, physicians should consider avoiding medications that are commonly associated with sedative AEs. Additionally, monitoring for the specific AEs listed in Table 2 is recommended to facilitate treatment compliance among females receiving psychiatric medications. The possible long-term AEs were mentioned at the symposium.

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