Use of Second-Generation Antipsychotics in Bipolar Disorder: A Practical Guide

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This practical guide is an update on the use of second-generation antipsychotics (SGAs) for the treatment of bipolar disorder. It reviews uses in bipolar depression, mania and maintenance treatment.

The focus is on FDA-approved indications, off-label uses are not discussed in this guide.

Table 1: Overview of SGAs approved for bipolar disorder

	Depression	Manic/mixed episodes	Maintenance
Aripiprazole		X	X
Asenapine		X	
Cariprazine		X	
Lurasidone	X		
Olanzapine		X	X
Olanzapine-fluoxetine combination	X		
Quetiapine (IR and XR)	X	X	X
Risperidone		X	
Risperidone LAI			X
Ziprasidone		X	

FDA- Approved Antipsychotics for Bipolar Depression

Clinical Points

- Bipolar I depression:
  - Three SGAs are FDA-approved for bipolar I depression: olanzapine-fluoxetine combination, quetiapine, and lurasidone.
  - Multiple trials have found no benefit in using aripiprazole and ziprasidone in bipolar I depression [1, 2].
- Bipolar II depression:
  - There are no FDA-approved treatments for bipolar II depression.
  - Quetiapine has evidence of efficacy for this use [3].
- General safety and tolerability principles:
  - The risk of extrapyramidal side effects and tardive dyskinesia is thought to be higher in bipolar disorder than schizophrenia [4].
  - Patients with bipolar depression may be more sensitive to side effects than patients with mania [5].

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Table 2: FDA-approved SGAs for bipolar I depression

Drug	Year approved	Initial dose and titration	Recommended dose	Maximum dose	Comments
Lurasidone	2013	20 mg once daily	20 -120 mg/day	120 mg/day	- Must be given with food (at least 350 calories) - Minimal metabolic effects - Risk of akathisia
Olanzapine-fluoxetine combination	2003	6 mg/25 mg (mg olanzapine/ mg equivalent fluoxetine) , once daily in the evening	Olanzapine 6 mg to 12 mg and fluoxetine 25 mg to 50 mg	18 mg of olanzapine and 75 mg of fluoxetine	- Olanzapine can cause significant weight gain and metabolic disturbances - Fixed doses limits dosing flexibility
Quetiapine	IR: 2006 XR:2008	Administer once daily at bedtime. Day 1: 50 mg Day 2: 100 mg Day 3: 200 mg Day 4: 300 mg	300 mg/day	300 mg/day	- A frequent patient complain is sedation and somnolence. Slow dose titration might help - Weight gain and metabolic disturbances are a concern

Second-Generation Antipsychotics for Mania and Mixed Episodes

Clinical Points

- Antipsychotics have specific antimanic properties that are independent of sedation [6] :
  - Non-sedative agents such as aripiprazole and ziprasidone can improve manic symptoms
  - Some clinicians confuse the sedating properties of olanzapine and quetiapine with an improved antimanic effect
- Both FGAs and SGAs are effective antimanic agents [7]:
  - None of the SGAs is more effective than haloperidol in reducing manic symptoms
  - All produce fewer extrapyramidal side-effects than haloperidol and are therefore more acceptable to patients.
- For patients with severe manic or mixed episodes: consider initial treatment with lithium or valproate plus an antipsychotic, rather than monotherapy.

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Table 3: FDA-approved SGAs for mania and mixed episodes (adults)

Drug	Year of FDA approval	Approval for manic episodes	Initial dose and titration	Recommended dose	Maximum dose
Asenapine	2009	- Monotherapy - Adjunctive therapy	- Monotherapy: 10 mg sublingually twice a day - Adjunctive: 5 mg sublingually twice a day	5 to 10 mg sublingually twice a day	10 mg sublingually twice a day
Aripiprazole	2004	- Monotherapy - Adjunctive therapy	- Monotherapy: 15 mg once daily - Adjunctive: 10 mg to 15 mg once daily	15 mg/dayw	30 mg/day
Cariprazine	2015	- Monotherapy	- Day 1: 1.5 mg once daily - Day 2: 3 mg once daily - Further dose adjustments can be made in 1.5 or 3 mg increments	3-6 mg/day	6 mg/day
Olanzapine	2000	- Monotherapy - Adjunctive therapy	- Monotherapy: 10 or 15 mg once daily - Adjunctive: 10 mg once daily	5 mg to 20 mg/day	20 mg/day
Risperidone	2003	- Monotherapy - Adjunctive therapy	- 2 to 3 mg per day - Increments of 0.5 or 1 mg per day	1-6 mg/day	6 mg/day
Quetiapine	2004	- Monotherapy - Adjunctive therapy	- Day 1: twice daily dosing totaling 100 mg - Day 2: twice daily dosing totaling 200 mg - Day 3: twice daily dosing totaling 300 mg - Day 4 : twice daily dosing totaling 400 mg - Dosage adjustments up to 800 mg/day by day 6 should be in increments of no greater than 200 mg/day	400-800 mg/day	800 mg/day
Quetiapine XR	2008	- Monotherapy - Adjunctive therapy	- Day 1: 300 mg/day - Day 2: 600 mg/day - Day 3: between 400 and 800 mg/day	400-800 mg/day	800 mg/day
Ziprasidone	2004	- Monotherapy	- Day 1: 40 mg twice daily with food - Day 2: 60mg or 80 mg twice daily with food	80-160 mg/day	160 mg/day

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Table 4: FDA-approved agents for mania and mixed episodes (children and adolescents)

Drug	Age	Initial dose and titration	Recommended dose	Maximum dose
Asenapine	10 years or older	- Starting dose: 2.5 mg sublingually twice a day - After 3 days: increase to 5 mg sunlingually twice daily - After additional 3 days: increase to 10 mg witce daily, as needed and tolerated	2.5 to 10 mg sublingually twice a day	10 mg sublingually twice a day
Aripiprazole	10 years or older	- Starting dose: 2 mg/day - After 2 days: 5 mg/day - After 2 additional days: 10 mg/day	10mg/day	10 mg/day
Olanzapine	Adolescents (ages 13-17)	- Starting dose: 2.5 mg or 5 mg	10 mg/day	20 mg/day
Quetiapine	10 years or older	- Day 1: 25 mg twice daily - Day 2: twice daily dosing totaling 100 mg - Day 3: twice daily dosing totaling 200 mg - Day 4 : twice daily dosing totaling 300 mg - Day 5 : twice daily dosing totaling 400 mg - Further dosage adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-600 mg/day.	400-600 mg/day	400-600 mg/ day
Risperidone	10 years or older	- Starting dose: 0.5 mg once daily - Dose may be increased at intervals of 24 hours or greater in increments of 0.5 mg or 1mg per day	1-6 mg/day	6 mg/day

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Table 5: FDA-approved intramuscular antipsychotics for agitation associated with bipolar I mania

Drug	Recommended dose	Efficacy shown in a dose range of:	Maximum dose	Comments
Aripiprazole	9.75 mg	5.25 to 15 mg	30 mg/day	- No additional benefit was demonstrated for 15 mg compared to 9.75 mg. - If agitation warranting a second dose persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given.
Olanzapine	10 mg	2.5 to 10 mg	30 mg/day	- In elderly patients and special clinical situations: a lower dose of 5 or 7.5 mg may be considered. - If agitation persists: subsequent doses up to 10 mg may be administered 2 hours after the first dose and 4 hours after the second dose. - Maximum number of doses: 3 doses in 24 hours; additional doses in patients with clinically significant postural hypotension are not recommended.

FDA- Approved Antipsychotics for Maintenance Treatment

Clinical Points

- Methodological limitations may favor second-generation antipsychotics as effective agents in maintenance treatment, these include [8]:
    - Lack of sufficient long-term follow-up
    - "Enriched" patient samples. Selection of patients with known response or tolerability to the investigational agent
- Even though clinical guidelines recommend some SGAs as first-line maintenance treatment, it is up to the prescriber to consider the risk of metabolic side effects in the long term.

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Table 6: FDA-approved SGAs for maintenance treatment in bipolar I disorder

Drug	FDA-approved as:	Dosing	Comments
Olanzapine	Monotherapy only	Continue treatment at the dosage required to maintain symptom remission Starting dose: 10 mg once daily Dose range: 5-20 mg/day Maximum dose: 20 mg/day	Good evidence for efficacy, but there are significant concerns about long-term metabolic effects.
Aripiprazole	Monotherapy Adjunctive therapy	Continue treatment at the dosage required to maintain symptom remission Starting dose for manic and mixed episodes: Monotherapy: 15 mg once daily Adjunctive: 10 mg to 15 mg once daily Target dose: 15 mg/day Maximum dose: 30 mg/day	Evidence from randomized trials suggests aripiprazole is more effective at preventing manic and mixed episodes than depressive episodes.
Quetiapine (IR and XR)	Quetiapine IR: Monotherapy only Quetiapine XR: Adjunctive therapy only	Continue treatment at the dosage required to maintain symptom remission Recommended dose for mania and mixed episodes: 400-800 mg/day. Recommended dose for bipolar depression: 300 mg/day	Efficacious for preventing manic and depressive relapses. Because of metabolic concerns, quetiapine needs to be carefully monitored.
Risperidone LAI (microspheres)	Monotherapy Adjunctive therapy	25 mg IM every two weeks Some patients may benefit from a higher dose of 37.5 mg or 50 mg	More efficacious in preventing mania relapses than depression. Found to be less effective in preventing overall relapse compared to olanzapine.
Ziprasidone	Adjunctive therapy only	Continue treatment at the dosage required to maintain symptom remission. Dose range: 80-160 mg/day	Recommended by CANMAT guidelines as first-line treatment, as adjunctive, not monotherapy. WFSBP guidelines: recommendation grade 3 (based on category “B” evidence: limited positive evidence from controlled studies).

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