Practical Guide to Long-Term Pharmacotherapy in Bipolar Disorder: An Updated Synthesis of Current Clinical Guidelines

Flavio Guzman, MD
Editor
Psychopharmacology Institute

About this guide: This guide reviews key data for the safe and effective prescription of drugs in the long-term treatment of bipolar disorder. All drugs are presented using the same format: evidence of efficacy, disadvantages and place in clinical guidelines. For some drugs we have included an additional section titled “comments”. Remember that clinical guidelines have their limitations and they are not a replacement for clinical judgment.
The guidelines summarized are the following:

**WFSBP 2012:**
- Group: World Federation of Societies of Biological Psychiatry
- Year updated: 2012

**CANMAT 2013:**
- Group: Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)
- Guideline title: Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013
- Year updated: 2013

**NICE 2014:**
- Group: National Institute for Health and Care Excellence (NICE)
- Guideline title: Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care
- Year updated: 2014

**BAP 2016:**
- Group: British Association for Psychopharmacology
- Guideline title: Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology
- Year updated: 2016
# Table of contents

03. Table of contents  
04. Before You Read the Evidence: A Warning About “Enriched” Study Designs  
05. A Summary of Drugs Used to Prevent Mood Episodes  
05. Lithium  
06. Lamotrigine  
07. Valproate  
08. Olanzapine  
09. Quetiapine  
10. Risperidone LAI  
11. Aripiprazole  
12. Ziprasidone  
13. Carbamazepine  
14. References
Before You Read the Evidence:  
A Warning About “Enriched” Study Designs

When interpreting the evidence derived from maintenance studies there is something important to consider: clinical trials often use “enriched” patient samples. There are two types of maintenance study designs: prophylaxis and relapse prevention [1].

• **Prophylaxis design:**
  “All comers” are included in the study. Any patient who is euthymic, no matter how that person got well, is eligible to be randomized to drug versus placebo or control.

• **Relapse prevention design:**
  Only those patients who acutely respond to the drug being studied are then eligible to enter the maintenance phase, which is when the study begins. Those who responded to the drug are then randomized to stay on the drug or be switched to placebo or control.

Most maintenance trials studying second-generation antipsychotics enroll individuals who have recently recovered from mania (relapse prevention). This enriched enrolled population has a greater proclivity toward manic recurrence than depressive recurrence. Only quetiapine and lamotrigine have been studied for individuals recovering from a depressive episode.
A Summary of Drugs Used to Prevent Mood Episodes

Lithium

Evidence of Efficacy
- Lithium is considered the gold standard for long-term maintenance therapy in bipolar disorder [2]
- It is the only mood stabilizer effective at reducing the risk of suicide [3]
- Monotherapy is ideal but often not adequate, and lithium can often be successfully combined with other adjunctive drugs such as lamotrigine or quetiapine [4]
- Several lines of evidence suggest that the benefit with lithium is greater for the prevention of manic episodes than it is for preventing depressive symptomatology [5]

Disadvantages
- Tolerability
- There is a high risk of recurrence on abrupt cessation [6]

Place in Clinical Guidelines

<table>
<thead>
<tr>
<th>Clinical Guideline</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFSBP 2012</td>
<td>Recommendation grade of 1 (best grade).</td>
</tr>
</tbody>
</table>

Comments
- Patients should not be deprived of lithium without a specific reason
- Side effects and risks are manageable if both the physician and the patient are well informed
- For patients who do not respond sufficiently to lithium, have contraindications or non-tolerable side effects, other mood stabilizers should be used
- Once-daily dosing at bedtime is better for treatment adherence (twice daily dosing gives sustained higher minimum concentrations, this has been linked to more pathological renal changes on biopsy)
Lamotrigine

Evidence of Efficacy
- Lamotrigine is most effective as a bipolar maintenance agent in patients who experience depressive-dominant bipolar disorder [7]
- May be appropriate for non-classic cases with mixed features or rapid cycling [8]

Disadvantages
- Slow titration (6 weeks) needed to decrease the risk of Stevens-Johnson syndrome
- Dose adjustment necessary if used in combination with valproate or carbamazepine

Place in Clinical Guidelines

<table>
<thead>
<tr>
<th>Clinical Guideline</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFSBP 2012</td>
<td>Recommendation grade of 1 (best grade), for patients tolerating lamotrigine where the predominant treatment goal is to prevent depressive recurrences or any episode.</td>
</tr>
<tr>
<td>CANMAT 2013</td>
<td>First-line treatment (limited efficacy in preventing mania).</td>
</tr>
<tr>
<td>NICE 2014</td>
<td>No specific mention to lamotrigine in long-term treatment.</td>
</tr>
</tbody>
</table>
| BAP 2016           | - Consider adding lamotrigine in depression-predominant bipolar disorder if lithium alone is ineffective.  
                      - Consider lamotrigine as monotherapy in bipolar II disorder when depression is the major burden. |
Valproate

Evidence of Efficacy

- While valproate has reported empirical efficacy, only a few trials support its long-term use.
- A recent review suggested that valproate may have superior tolerability compared to lithium for some patients [9].
- About the **BALANCE study** [10]:
  
  **Results**
  - Lithium was superior to valproate.
  - The combination of lithium and valproate was more effective than valproate monotherapy in preventing depressive recurrences.

  **Comments**
  - This study had a methodological limitation: an open design.
  - The results show the importance of combination treatment in some patients.

Disadvantages

- Should be avoided during pregnancy due to teratogenicity risk.
- Should not usually be considered for women of child-bearing potential [11].

Place in Clinical Guidelines

<table>
<thead>
<tr>
<th>Clinical Guideline</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFSBP 2012</td>
<td>Recommendation grade of 3 (1 is the best), limited positive evidence from controlled studies.</td>
</tr>
</tbody>
</table>
| NICE 2014          | - No longer recommended as first-line treatment.  
|                    | - The updated guidelines recommend valproate as second-line treatment if lithium is poorly tolerated or unsuitable. |
| BAP 2016           | If lithium alone is ineffective, consider combination treatment with valproate. If lithium is poorly tolerated or unsuitable, consider valproate among other options. |
Olanzapine

Evidence of Efficacy

- Meta-analysis of five RCTs by Cipriani and cols [12]

Results:
- Olanzapine was effective as adjunct to lithium or valproate in preventing manic, but not composite outcomes of all mood episodes

Comments:
- Olanzapine may prevent further manic episodes only in patients who have responded to olanzapine in an acute manic or mixed episode and who had not previously responded to lithium or valproate

Disadvantages

- Risk of metabolic side effects: weight gain, increased risk of type II diabetes, increased cholesterol and triglycerides

Place in Clinical Guidelines

<table>
<thead>
<tr>
<th>Clinical Guideline</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFSBP 2012</td>
<td>Recommendation grade of 2 (the best grade is 1). This grade means there is full evidence from controlled studies, but a moderate risk-benefit ratio.</td>
</tr>
<tr>
<td>CANMAT 2013</td>
<td>First-line treatment, mainly for the prevention of mania.</td>
</tr>
<tr>
<td>NICE 2014</td>
<td>Recommended if lithium is poorly tolerated or is not suitable.</td>
</tr>
<tr>
<td>BAP 2016</td>
<td>No specific recommendation for olanzapine. If lithium is poorly tolerated or unsuitable, consider other options: dopamine antagonists/partial agonists.</td>
</tr>
</tbody>
</table>

Comments

- Good evidence of efficacy, but there are significant concerns about long-term side effects
Quetiapine

Evidence of Efficacy
- Quetiapine has shown efficacy in randomized controlled trials as monotherapy and adjunctive therapy [13]
- It is efficacious for preventing manic and depressive relapses [14]
- Short-term studies suggest it may be a good option for patients with mixed features, rapid cycling and sleep deficits [15]

Disadvantages
- Risk of metabolic side effects

Place in Clinical Guidelines

<table>
<thead>
<tr>
<th>Clinical Guideline</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFSBP 2012</td>
<td>Recommendation grade of 1. Evidence base for quetiapine is “quite outstanding”.</td>
</tr>
<tr>
<td>CANMAT 2013</td>
<td>Recommended as first-line monotherapy and as adjunctive therapy with lithium or divalproex.</td>
</tr>
<tr>
<td>NICE 2014</td>
<td>Consider quetiapine if it has been effective during an episode of mania or bipolar depression and if lithium is poorly tolerated or not suitable.</td>
</tr>
<tr>
<td>BAP 2016</td>
<td>If lithium alone is ineffective, consider combination treatment with quetiapine (recommended for depression predominant bipolar disorder).</td>
</tr>
</tbody>
</table>

Comments
- Metabolic concerns warrant careful monitoring
- Efficacy shown for preventing manic and depressive episodes
Risperidone LAI

Evidence of Efficacy

- Risperidone long-acting injection has been shown to improve outcomes and reduce the risk of manic recurrence [15]
- Similar to olanzapine, risperidone was more efficacious in preventing mania relapses than depression, however, it was found to be less effective in preventing overall relapse compared to olanzapine [16]

Disadvantages

- Metabolic side effects
- Hyperprolactinemia

Place in Clinical Guidelines

<table>
<thead>
<tr>
<th>Clinical Guideline</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFSBP 2012</td>
<td>Recommendation grade of 2 (the best grade is 1).</td>
</tr>
<tr>
<td>CANMAT 2013</td>
<td>First-line treatment both as monotherapy and as adjunct to lithium or valproate.</td>
</tr>
<tr>
<td>NICE 2014</td>
<td>No specific mention.</td>
</tr>
<tr>
<td>BAP 2016</td>
<td>Consider long-acting formulations if prophylaxis against recurrence of mania is required and adherence to oral medication is erratic or injection preferred.</td>
</tr>
</tbody>
</table>
Aripiprazole

Evidence of Efficacy

- Aripiprazole is efficacious as monotherapy and as adjunctive treatment [17]
- Evidence from randomized trials suggests aripiprazole is more effective at preventing manic and mixed episodes than depressive episodes [18]

Disadvantages

- Risk of akathisia

Place in Clinical Guidelines

<table>
<thead>
<tr>
<th>Clinical Guideline</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFSBP 2012</td>
<td>- Recommendation grade of 1. However, this applies only to patients with an index episode of mania and acute response to aripiprazole.</td>
</tr>
<tr>
<td></td>
<td>- For all other groups of patients, long-term use is not supported by solid evidence, but should not be excluded in specific clinical scenarios such as: non-response, tolerability or safety problems with other long-term treatments.</td>
</tr>
<tr>
<td>CANMAT 2013</td>
<td>First-line treatment as monotherapy and as adjunctive therapy with lithium or valproate.</td>
</tr>
<tr>
<td>NICE 2014</td>
<td>No specific mention.</td>
</tr>
<tr>
<td>CANMAT 2013</td>
<td>- Dopamine antagonists/partial agonists may be appropriate for the long-term management of bipolar patients especially where non-mood-congruent psychotic features are prominent.</td>
</tr>
<tr>
<td></td>
<td>- Dopamine antagonists/partial agonists may be useful in difficult-to-treat cases of rapid cycling.</td>
</tr>
</tbody>
</table>
Ziprasidone

Evidence of Efficacy

- There is evidence from one randomized controlled trial supporting the use of ziprasidone as adjunctive maintenance treatment [19]
- Use as monotherapy is not supported by evidence.

Disadvantages

- As is the case with other SGAs (olanzapine, risperidone LAI and aripiprazole) ziprasidone is efficacious for the prevention of mania but not for the prevention of depressive episodes.

Place in Clinical Guidelines

<table>
<thead>
<tr>
<th>Clinical Guideline</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFSBP 2012</td>
<td>Recommendation grade 3 (the best grade is 1). This grade is based on Category “B” evidence (limited positive evidence from controlled studies).</td>
</tr>
<tr>
<td>CANMAT 2013</td>
<td>- Recommended as first-line treatment as adjunctive therapy with lithium or valproate.</td>
</tr>
<tr>
<td></td>
<td>- Not recommended as monotherapy.</td>
</tr>
<tr>
<td>NICE 2014</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>BAP 2016</td>
<td>No specific recommendation.</td>
</tr>
</tbody>
</table>
Carbamazepine

Evidence of Efficacy

- Effectiveness in clinical practice is not as robust as other first-line treatments such as lithium [20].
- There is evidence suggesting greater efficacy in patients with bipolar II disorder compared to those with bipolar I disorder. However, these data are derived from post-hoc analyses and are limited by small sample size [21].

Disadvantages

- Clinical usefulness is limited by tolerability and drug interaction potential.

Place in Clinical Guidelines

<table>
<thead>
<tr>
<th>Clinical Guideline</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFSBP 2012</td>
<td>Recommendation grade of 3 (the best grade is 1). This grade is based on Category “B” evidence (limited positive evidence from controlled studies).</td>
</tr>
<tr>
<td>CANMAT 2013</td>
<td>Second-line treatment both as monotherapy and as adjunctive with lithium or valproate.</td>
</tr>
<tr>
<td>NICE 2014</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>BAP 2016</td>
<td>Less effective than lithium, has little if any effect on relapse to depression and is liable to interfere with the metabolism of other drugs.</td>
</tr>
</tbody>
</table>
References


