

### Appendix 3. Evidence-based Pharmacotherapy Recommendations for Bipolar I Disorder

ACUTE MANIA phase	
AGENTS	COMMENTS and TIPS IN TREATMENT
<b>Lithium</b> (e.g., Carbolith®)	Classic symptoms of mania and previous response to lithium predict a positive response to lithium Starting dose of 300 mg BID or 600-900mg HS, increased every 4-7 days to reach a target blood level of 0.8-1.2 mmol/L (0.6-1.0 meq/L). Check blood levels after each dose increase and before increasing dose again. As blood levels near the upper end of the therapeutic range (>1.0 meq/L), check more often to reduce the risk of toxicity. Usual maintenance dose is 900-1800 mg/day
<b>Divalproex</b> (Epival®, Depakote®)	Rapid cycling and mixed mania (prominent depressive symptoms during mania) are associated with better response to divalproex than lithium. Start with 400-800 mg/day. Check serum level after 5 days; aim for level of 300-800 micromol/L
<b>Atypical Antipsychotics</b> <b>Olanzapine</b> (Zyprexa®) <b>Risperidone</b> (Risperda®) <b>Quetiapine</b> (Seroquel®) <b>Aripiprazole</b> (Abilify®) <b>Ziprasidone</b> (Zeldox®)	Atypical antipsychotics (AAP) appear equally effective in patients with or without psychotic features.
<b>Combinations</b> <b>Lithium + risperidone or quetiapine</b> <b>Divalproex + risperidone or quetiapine</b> <b>Lithium + olanzapine</b> <b>Divalproex + olanzapine</b>	Combination therapy is the treatment of choice in patients with severe manic or mixed episodes that impair functioning, especially when behaviour is aggressive or potentially harmful.
ACUTE DEPRESSION phase	
<b>Lithium</b> <b>Lamotrigine</b> <b>Quetiapine</b> Lithium + SSRI <b>Divalproex + SSRI</b> <b>Olanzapine + SSRI</b> <b>Lithium + divalproex</b> <b>Lithium + bupropion (Wellbutrin®)</b> <b>Divalproex + bupropion</b>	No systematic evaluation of response predictors has been performed, although the history of manic and depressive episodes can help guide medication choices. Pharmacotherapy that does <u>not</u> include an antidepressant is appropriate for patients with rapid cycling or severe mania, but may take 4-6 weeks for antidepressant effects to develop. For patients with severe depression and mild mania, a combination of a mood stabiliser and an antidepressant is appropriate. SSRIs and bupropion are preferable to other antidepressants. Antidepressants should <u>not</u> be used alone, as may induce rapid cycling or mania/hypomania; withdraw them after 2-3 months. For patients receiving maintenance therapy who experience a mild depression, cognitive behavioural therapy (CBT) or psychosocial strategies may be considered before adding a medication.
MAINTENANCE phase	
<b>Lithium</b> <b>Lamotrigine</b> <b>Divalproex</b> Olanzapine	Lithium remains first-line agent to prevent relapse of both depression and mania in bipolar disorder. Unfortunately, non-adherence is common. Rapid discontinuation increases the risk of relapse and of suicide. Other agents may be more effective when rapid-cycling (at least four episodes/year).

\***Bold indicates Level I-1 evidence; bold and italics indicates level I-2 evidence**

**Sources:**

1. Yatham LN, Kennedy SH, O'Donovan C, Parikh S, MacQueen G, McIntyre R et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. *Bipolar Disord* 2005; 7 Suppl 3:5-69 PM:15952957; 2. Stovall J. Bipolar disorder. [www.uptodate.com](http://www.uptodate.com). 14.2. 2006. 3. Yatham LN, Kennedy SH. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. *Bipolar Disord* 2006; 8:721-739. 4. Scottish Intercollegiate Guidelines Network. Bipolar affective disorder. A national clinical guideline. Scottish Intercollegiate Guidelines Network 2005 Available from: URL:<http://www.sign.ac.uk/guidelines/published/index.html>; 5. Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder. *Aust N Z J Psychiatry* 2004; 38(5):280-305 PM:15144505

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