Summary of the evidence base for mood disorder pharmacotherapy

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Medication	Bipolar I Mania		Bipolar I Depression		Bipolar II Depression		Unipolar MDD		Acute Depressive Mixed state
	Acute episode	Relapse Prevention	Acute episode[R]	Relapse Prevention	Acute episode	Relapse Prevention	Acute episode[g]	Relapse Prevention	
AD monotherapy			−/∅[a,b]	∅[a]	±/∅[a,c]	±/∅[a,d]	+++	+++	
AD adjunct to MS			(±/∅)[a,e]	(±/∅)[a,f]	(±/∅)[a,e]	(±/∅)[a,f]	See below	See below	
Lithium	+++	+++[o,t]	±[U]	±[o,t]	±[U]	−[H]	(±)[F]	(±)	
Valproate (Epival®)	+++	±	+[z]	±[J]	−[V]	+	+	(+)	
Lamotrigine (Lamictal®)	−[L]	±[m,L]	±[K,L]	+++[m,L]	−	++[G]	(−)[L]	(+)	
Olanzapine (Zyprexa®)	+++	++[B]	+++,(+)[i]	±[B]	+		(±)[j]	(+)[k,h]	
Risperidone (Risperdal®)	+++	++[I]	±	−[I]	(+)	(+)	(+++)	(+)[h]	
Quetiapine (Seroquel IR/XR®)	+++[n]	+++, (+++)[o]	+++[p]	+++, (+++)[o,E]	+++[q]	+++[E]	+++ (+++)[r]	++[s] (++)[,h]	
Ziprasidone (Zeldox®)	+++	(++)[u]	−,(−)[v]	(−)[u]	+[w]		−,(++)[O]		++[W]
Aripiprazole (Abilify®)	+++[x]	+++[A]	±[y]	−[A]	(+)[X]		(+++)[S]	(+)[T,h]	
Paliperidone ER (Invega®)	+++[C]	++[M]		−[M]					
Asenapine (Saphris®)	+++,(++)[D]	+++[D]							
Lurasidone (Latuda®)			++,(++)[N]	+,(++)[P]			(+)[Y]		++[Q]
Brexpiprazole (Rexulti®)							(+++)[Z]		

Abbreviations:

+ve = positive; AD = antidepressant; adj = adjunctive; BD = Bipolar disorder; BI/II = bipolar I/II; MDD = Major Depressive Disorder; MS = mood stabilizers; NNT = number needed to treat (to achieve one extra responder vs PBO tx); OFC = olanzapine-fluoxetine combination; OL = open-label; PBO = placebo; pt =patient; RPCT = randomized placebo-controlled trial; tx =treatment; sig'ly = significantly; stat sig = statistically significant; TRD = tx-resistant depression

Legend:

( )	Brackets indicate that the rating refers to trials that tested the medication as an adjunct
∅	Some evidence of harm
−	Evidence of lack of statistically significant advantage over placebo
±	Conflicting or equivocal evidence
+	Low level evidence, but mostly positive [naturalistic data, open label trials, crossover trials or very small (n ≤ 30) placebo-controlled trials]
++	Single positive randomized double-blind placebo-controlled trial (RPCT) of adequate size
+++	Replicated positive RPCTs of adequate size

Footnotes:

a	Although the evidence is mixed, inconclusive, and controversial, ADs may be associated with mood switching, new or worsening irritability and agitation, suicidal ideas, new-onset insomnia, impulsivity, cycle acceleration. **Non-AD tx should be considered as monotx first,** however AD tx may be considered **as adjunct to MS** when there is a history of previous positive response to ADs, but should be avoided in mixed or rapid cycling depression (*Pacchiarotti I et al. The ISBD Task Force report on AD Use in Bipolar Disorders. Am J Psychiatry 2013;170:1249-62*).
b	3 RPCTs (including the largest one, EMBOLDEN II; see footnote p) reported negative results for paroxetine monotherapy.
c	AD monotx in BII dep is controversial: some reports have suggested benefit, others not. Switch rates were 4-5%, but subsyndromal hypomania was noted in ≅ 20% in a 14 week open-label fluox trial (see discussion in *Amsterdam JD, Shults J. J Clin Psychopharmacol 2010;30:306-311*).
d	In an enriched group design, BII patients who had responded to fluoxetine monotx had a longer time to relapse and a trend (but not stat sig) for better relapse prevention when continuing fluox vs switch to placebo (p = 0.1) (Amsterdam JD, Shults J. Am J Psychiatry 2010;167:792-800).
e	Although OFC appears effective (see footnote i), in the largest RPCT (STEP-BD), adding bupropion or paroxetine to MS for depressed BI/II pts was not better than adding placebo (*Sachs GS et al. N Engl J Med 2007;356:1711-1722*). Other data and meta-analyses are inconsistent.
f	In the STEP-BD study, depressed BI/II pts who had responded to AD + MS in acute tx were randomized to continue the combination or switch gradually to PBO + MS. At 1-year outcome, there was no clear benefit of AD *(Ghaemi SN et al. J Clin Psychiatry 2010:71(4):372-380),* but at 3-yr outcome, those who continued the AD had slightly less depressive relapses (more benefit in BI than BII pts), but more manic relapses (worse in the BI than BII pts). [*Vöhringer PA et al. J Clin Psychopharmacol Oct 2015;35:605-608*]. Other trials were ambiguous, inconclusive.
g	In USA, the only meds with regulatory approval for adj tx of MDD are Ari, QXR, OFC, and Brex (*Citrome L. J Clin Psychopharmacol 2017;37(2):138-147*) but In Canada, only Ari has regulatory approval for adj tx (Quet XR is approved as monotx, but not as adj tx) in MDD
h	In a large population-based mirror-image study of MDD pts receiving at least 8 weeks of adj tx, psych hospitalization rates were reduced (in the year after vs. the year before adj tx) by 74% (Risp); 68% (Ari); 50% (Quet); 38.5% (Olz) (*Lin CY et al. J Clin Psychiatry 2014;75(9);e924-931*)
i	NNT (for both response and remission) = 4 for OFC, but only 11-12 for Olanzapine monotx. Significant weight gain (i.e. ≥ 7%) noted with both OFC and Olanz monotx (NNH = 5) (*Tohen M et al. Arch Gen Psychiatry 2003;60(11):1079-88;Tohen M et al. Br J Psychiatry 2012;201:376-382*)

j	OFC was not significantly better than fluoxetine or olanzapine monotx in 4/5 RCTs of TRD, but an integrated analysis found a small but stat sig advantage for OFC. Remission rates: OFC: 25.5%, Olz; 17.3%, Fluox: 14% (*Trivedi MH et al. J Clin Psychiatry 2009;70(3):387–396*).
k	76 wk open-label study: 75% of TRD maintained remission, but 31% had ≥10% wt gain *(Corya SA et al. J Clin Psychiatry 2003;64:1349-56)*
l	2 long-term RPCTs (*Quiroz JA et al. Biol Psychiatry 2010;68(2);156-162* and *Vieta E et al. Eur Neuropsychopharmacol 2012;22(11):825-35*)
m	BI manic (*Bowden et al. Arch Gen Psychiatry 2003;57:481-489*) or dep pts (*Calabrese et al. J Clin Psychiatry 2003;64:1013-1024*) stabilized on Lam and then randomized to continue this tx found it effective for prolonging time to a dep (but not manic) episode (at 200 but not 50 mg/day).
n	Dose range: 400-800 mg/day. Target dose: 600mg/day [evidence reviewed in: *Janicak PG, Rado JT; Expert Opin Pharmacother (May 2012)*]
o	BI pts stabilized on Quet (300-800 mg/d) and then randomized to continue this monotx (median dose = 546 mg/d) had sig'ly increased time to any mood, manic or dep event (as did those switched to Lithium) vs PBO *(Weisler RH et al. J Clin Psychiatry 2011;72(11):1452-64)*. Same effect in trials of Quet add-on to Li or Val *(Vieta E et al. J Affect Disord 2008;109(3):251-256; Suppes T et al. Am J Psychiatry 2009;166(4):476-488* **).**
p	Quetiapine IR: both 300 mg and 600 mg were effective in 4 studies: BOLDER I & II *(Calabrese JR et al. Am J Psychiatry 2005;162:1351-1360; Thase ME et al. J Clin Psychopharmacol 2006;26:600-609; Weisler RH et al. J Clin Psychiatry 2008; 69:769-782);* EMBOLDEN I (vs. Li: *Young AH et al. J Clin Psychiatry 2010;71(2):150-162),* EMBOLDEN II (vs. Parox: *McElroy SL et al. J Clin Psychiatry 2010;71(2):163-174*). Quetiapine XR: 300 mg (only dose tested) was effective in the RPCT using XR form *(Suppes T et al J Affect Disord 2010 ;121(1-2) :106-1152).*
q	Pooled data from BOLDER I AND II *(Suppes T et al. World J Biol Psychiatry 2008;9(3):198-221)* and data from EMBOLDEN II (see footnote p) show statistically significant efficacy relative to PBO, however this was not achieved in EMBOLDEN I probably due to the small n of BII pts.
r	4 +ve RPCTs with Quetiapine XR: 2 as add-on tx and 2 as monotx for MDD [*Weisler RH et al. Int Clin Psychopharmacol 2012;27(1):27-39*]
s	RPCT involved Quetiapine XR 50-300 mg (median dose = 177 mg) [*Liebowitz M et al. Depress Anxiety 2010;27:964-976*].
t	Although individual RPCTs are mostly -ve, a meta-analysis [*Severus E et al. Int J Bipolar Disord 2014;2(15)*] and network meta-analysis *(Miura T et al. Lancet Psychiatry 2014;1:351-9)* found Li to be sig'ly better than PBO for prevention of manic and, to a lesser extent, depressive relapses.
u	A 6-month maintenance RPCT of Ziprasidone (vs PBO) as an adjunct to Li or Val (for manic or mixed pts stabilized on the combination prior to randomization) showed significantly longer time to manic, but not depressive, relapse (*Bowden CI et al. J Clin Psychiatry 2010;71(2):130-137*).
v	3 -ve 6-wk RPCTs: 2 monotx (*Lombardo et al. J Clin Psychopharm 2012;32(4):470-8*),1 adj tx (*Sachs et al. J Clin Psych 2011;72(10):1413-22*)
w	8-wk open-label trial in 20 pts. Mean dose at study end: 58 mg/day (*Liebowitz MR et al. J Affect Disord 2009;118:205-208*)
x	15-30 mg daily (*Keck PE et al. J Affect Disord 2009;112(13):36-49; Young AH et al. Br J Psychiatry 2009;194(1):40-48*)
y	2 –ve RPCTs (*Thase ME et al. J Clin Psychopharmacol 2008;28(1):13-20)* used 5 to 30 mg/d doses. Pooling produced a +ve result with a small effect size = 0.17 but the response rate was not sig better than PBO (NNT = 44) (*Fountoulakis KN et al. J Affect Disord 2011;133:361-370*). Lower doses (< 15 mg per day) may be more antidepressant than higher doses (see *Katzman MA, Kjernisted K. Can J Diagnosis Feb 2010*).
z	Meta-analysis of 4 small RPCTs was +ve overall with NNT = 7 for response and also for remission, but the total sample size was small (n=142), different definitions of response were used, and so the evidence was termed "preliminary" (*Bond DJ et al. J Affect Disord 2010;124:228-234).*
A	Manic or mixed pts stabilized on Aripiprazole 15 or 30 mg/day and then randomized to continue (vs switch to PBO) had less manic relapses and longer time to manic relapse, but no benefit re: depressive relapse after 26 wks *(Keck PE et al. J Clin Psychiatry 2006;67:626-637)* or after 100 wks (*Keck PE et al. J Clin Psychiatry 2007;68:1480-1491*). However, few pts in these studies (even in the PBO group) had depressive relapses. Similar results with Aripiprazole 400 mg once-monthly injections (*Calabrese JR et al. J Clin Psychiatry published online Jan 31, 2017*)
B	Manic or mixed episode pts stabilized on Olanzapine for ≥2 wks had less manic relapses when randomized to continue Olanz vs switch to PBO, but the prevention of depressive (p=.08) or mixed (p=.1) relapses did not reach stat. sig *(Tohen M et al. Am J Psychiatry 2006;163(2):247-256)*
C	In a 3-wk RPCT comparing 3, 6 and 12 mg doses in acutely manic or mixed pts, only the 12mg dose was sig'ly better than PBO *(Berwaerts J et al. J Affect Disord 2012;136,e51-e60).* A flexible dose (3-12 mg/day) RPCT was also +ve (*Vieta E et al. Bipolar Disord 2010;12:230-243*)
D	Starting doses: 10 mg BID (as monotx); 5mg BID (as adjunct). Comparable efficacy for Asenapine and Olanzapine in two 3-wk double-blind PBO-controlled monotx trials; 9-wk and 40-wk extension trials also found Ase = Olz *(Vita A et al. Int Clin Psychopharmacol 2013 ;28:219-227).* One +ve 12-wk RPCT as adj in incompletely responsive Li- or Val- treated pts *(Szegedi A et al. J Clin Psychopharmacol 2012;32:46-55*).
E	In the EMBOLDEN I & II trials, BI/II depressed pts responding to Quet IR 300 or 600mg/day in the acute phase who were then randomized to continue this Rx (vs switch to PBO) had sig'ly less risk of depressive events *(Young AH et al. World J Biol Psychiatry 2014 Feb;15(2):96-112)*
F	The data for Li augmentation of antidepressants involves mainly TCAs and included bipolar depressed pts in the samples. Evidence for Lithium's efficacy as augmentation of modern antidepressants in unipolars is weak, equivocal *(Crossley NA, Bauer M. J Clin Psychiatry 2007;68:935-40)*
G	In rapid cyclers who responded to Lam, 28% less relapses over 6 mo if tx continued vs pbo (*Calabrese JR et al. J Clin Psych 2000;61:841-850*)
H	BII depressed pts who responded to fluoxetine monotherapy in acute treatment and were then randomized to switch to Lithium monotherapy had no relapse-prevention benefit vs PBO in a 50-week continuation study (*Amsterdam JD, Shults J. Am J Psychiatry 2010;167:792-800*)
J	In a 52-week RPCT, valproate did not separate from placebo on the primary outcome of time to depressive relapse *(Bowden CL et al. Arch Gen Psychiatry 2000;57:481-9*) but secondary analyses indicated that pts who had responded to Val when manic had less depressive morbidity and relapse in maintenance when continuing Val vs switch to placebo *(Gyulai L, Bowden CL et al. Neuropsychopharmacology 2003;28:1374-1382)*
K	None of the 5 RPCTs showed sig results on the primary outcomes, but meta-analysis yielded significant albeit modest response rates (NNT=12), but in more depressed pts (initial HRSD scores >24), NNT = 7. Most pts received 200 mg/d. (*Geddes JR et al. Br J Psychiatry 2009;194:4-9*). Lam improves dep cognition and psychomotor slowing but not wt gain, sleep, energy or anxiety (*Mitchell et al. CNS Spectrums 2013;18:214-24*).
L	See comprehensive review: *Bowden CL, Singh V. Lamotrigine for the tx of bipolar disorder. Expert Opin Pharmacother 2012;13(17):2565-71*
M	RPCT of manic or mixed episode pts who remitted on Paliperidone ER: pts randomized to continue it in maintenance tx had a longer time to recurrence of manic (but not dep) symptoms compared to those switched to placebo (*Berwaerts J et al. J Affect Disord 2012;138:247-258*).
N	2 +ve 6 wk RPCTs: as monotx (NNT = 5) and as adj to Li or Val (NNT = 7) [*Loebel A et al. Am J Psychiatry 2014;17(2):160-168 and 169-177*]
O	One -ve RPCT as monotx in MDD (*Papakostas GI et al. J Clin Psych 2012;73(12):1541-7);* one +ve RPCT as adjunct to escitalopram for TRD with NNT=7 for Ham-D response and NNT=4 for Ham-A response; NNH =10 for intolerance *(Papakostas et al. Am J Psych 2015;172(12):1251)*
P	A 28-wk RPCT of continued adj Lurasidone (mean dose = 54 mg/d + Li or Val) found a sig'ly longer time to dep episode recurrence. *(Calabrese J et al. Neuropsychopharmacology 2015;40;S479-480).* Also, in a 6-month open label extension of the RPCTs cited in footnote N, pts continuing Lurasidone (modal dose = 60 mg/d) improved further (5 more points on MADRS). (*Ketter T et al. Depression and Anxiety 2016;00:1–11).*
Q	A +ve 6-wk RPCT for MDD + 2-3 manic symptoms (NNT for response = 3; remission = 4) [*Suppes T et al. Am J Psychiatry 2016;173(4):400*].
R	The only Health Canada-approved medications for acute bipolar depression are Quetiapine (IR, XR) and Lurasidone
S	3 large RPCTs demonstrated efficacy as adjunct to antidepressants for treatment-resistant depression (after failure of 2 to 4 AD trials): *Berman et al. J Clin Psychiatry 2007;68:843-53; Berman et al. CNS Spectr 2009;14:197-206; Marcus et al. J Clin Psychopharmacol 2008;28:156-65*
T	Improvement with adjunctive aripiprazole was sustained in a 52-wk OL trial *(Berman et al. Neuropsych Disease and Treatment 2011;7:303-312)*
U	There is "almost no evidence" (only old, very small crossover trials) supporting lithium for the acute tx of bipolar depression (*Bhagwagar Z, Goodwin GM. Clin Neurosci Res 2002;2:222-7*). EMBOLDEN I (see footnote p) was –ve, but mean serum conc of Lithium was only 0.61 mEq/l*).*
V	Valproate = placebo in the Bipolar II subgroup in the trial by *Muzina DJ et al. J Clin Psychiatry 2011;72(6):813-819*
W	+ve 6-wk RPCT for mixed depression in MDD or BII pts (NNT for response = 4; for remission = 3) [*Patkar A et al. PLoS ONE 2012;7(4): e34757*]
X	Chart review of BII/NOS pts on other Rx: improved when ari 1-5 mg/d added (*Kelly T, Lieberman DZ. J Clin Psychopharmacol 2017;37:99-101*)
Y	Case report study (n = 4) of benefit by adding Lur to antidepressant and MS (*Nuñez NA, Gobbi G. Psychopharmacology 2017;37(2):263-4*)
Z	A RPCT using 2 mg and a second RPCT using 1 or 3 mg (*Thase et al. J Clin Psychiatry 2015;76(9):1224-31* and *1232-40* respectively)