Summary of the evidence base for mood disorder pharmacotherapy

Eric Teboul MD, CM July 2022 ericteboul@videotron.ca

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

Abbreviations:

+ve = positive; -ve = negative; AD = antidepressant; adj = adjunctive; BD = Bipolar disorder; BI/II = bipolar I/II; conc = concentration; dep = depressed; LAI = Long-acting injection; Lam = Lamotrigine; Li = Lithium; MDD = Major Depressive Disorder; maint = maintenance; mo = month; monotx = monotherapy; MS = mood stabilizers; NNT = number needed to treat (to achieve one extra responder in treatment group vs PBO group); OFC = olanzapine-fluoxetine combination; OL = open-label; Olz = Olanzapine; PBO = placebo; pt(s) = patient(s); QXR = Quetiapine XR; RPCT = randomized placebo-controlled trial; sig('ly) = significant(ly); stat sig = statistically significant; TCA = tricyclic AD; TRD = treatment-resistant depression; tx = treatment; wks = weeks; wt = weight

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 RPCT of adequate size; +ve meta-analysis/pooling of studies; +ve post hoc analysis of pooled studies
+++	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 monotherapy first;** AD may be considered **as an adjunct to MS** when there is a history of previous +ve response to AD, 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 monotherapy 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-wk OL fluox trial (see discussion in *Amsterdam JD, Shults J. J Clin Psychopharmacol 2010;30:306-311*).
d	In an enriched group design, BII pts who had responded to fluoxetine monotherapy had a longer time to relapse and a trend (but not stat sig) for better relapse prevention when continuing fluox vs switch to PBO (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 fewer 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*). In Canada, only Ari has regulatory approval for adj tx in MDD (Quet XR is approved as monotherapy, but not as adj tx)
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 monotherapy. Significant wt 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 monotherapy in 4 of 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 LAI **monotx** RPCTs (*Quiroz JA et al. Biol Psychiatry 2010;68(2);156-162* and *Vieta E et al. Eur Neuropsychopharmacol 2012;22(11):825-35*); one **adj** LAI RPCT (*Macfadden W et al. Bipolar Disord. 2009;11:827-39*); one **adj oral** RPCT (*Yatham LN et al Mol Psychiatry. 2016;21:1050-6*)
m	Network meta-analysis found Lam effective for prevention of dep (but not manic) relapses *(Miura T et al. Lancet Psychiatry 2014;1:351-9)*
n	See systematic review and meta-analysis of maint tx with 2nd gen antipsychotics for BD: *Lindström L et al. J Affect Disord 2017;213:138-150*
o	Quetiapine responders randomized to continue it or switch to Li both had sig'ly increased time to any mood relapse vs PBO *(Weisler RH et al. J Clin Psychiatry 2011;72(11):1452-64).* Same with Quetiapine adj to Li or Val *(Suppes T et al. Am J Psychiatry 2009;166(4):476-488* **).**

p	Quetiapine 300 and 600 mg were effective in 4 RPCTs [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);* EMBOLDEN I (vs. Li: *Young AH et al. J Clin Psychiatry 2010;71(2):150-162)* and EMBOLDEN II (vs. Parox: *McElroy SL et al. J Clin Psychiatry 2010;71(2):163-174*)] as was QXR 300 mg *(Suppes T J Affect Disord 2010 ;121(1-2) :106-15).*
q	Pooled data from the 4 acute bipolar dep RPCTs cited in footnote p found stat sig efficacy in BII (*Young AH et al. Int J Bipolar Disord 2013;1:10*)
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	6-mo RPCT of Zip adj to Li or Val found sig'y longer time to manic, but not dep, relapse (*Bowden CI et al. J Clin Psychiatry 2010;71(2):130-7*).
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 Ari 15 or 30 mg/d who continued this tx (vs switch to PBO) had less manic (but not dep) relapses after 26 wks *(Keck PE et al. J Clin Psychiatry 2006;67:626-637)* and after 100 wks (*Keck PE et al. J Clin Psychiatry 2007;68:1480-1491*). However, few pts (even in the PBO group) had dep relapses. Similar results with Ari LAI (*Calabrese JR et al. J Clin Psychiatry 2017;78(3):324-31*)
B	Manic or mixed episode pts stabilized on Olz for ≥ 2 wks had less manic relapses when randomized to continue Olz 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).* In the network meta-analysis cited in footnote m, Olz was sig'ly better than PBO in the prevention of manic but not dep relapse or recurrence.
C	In a systematic review and network meta-analysis, although all agents rated +++ were effective for manic symptoms, only ari, olz, quet, and risp had better acceptability (lower all-cause discontinuation) than placebo (*Kishi T et al. Mol Psychiatry. 2022; 27(2): 1136–1144*)
D	Starting doses: 10 mg BID (as monotx); 5mg BID (as adjunct). Comparable efficacy for Ase and Olz in two 3-wk monotx RPCTs. One +ve 12-wk RPCT as adj treatment *(Szegedi A et al. J Clin Psychopharmacol 2012;32:46-55*). Manic or mixed pts stabilized on Ase and then randomised to Ase (vs PBO) for 26-wk maint tx had less manic (NNT = 7) and dep (NNT = 16) recurrences (*Szegedi A et al. Am J Psychiatry 2018:175:71-79*)
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;15(2):96-112).*
F	An OL study of Li as **monotx** found a response rate of 68% in **recurrent** dep but 0% in single episode dep (*Bschor T, Bauer M. Curr Pharm Des 2006;12(23):2985-92*). Studies of Li **adj** to ADs used mainly TCAs and many included **bipolars**. Evidence for Li as add-on tx with modern ADs in **unipolar** dep is weak, equivocal *(Crossley NA, Bauer M. J Clin Psychiatry 2007;68:935-40; Connolly KR, Thase ME. Drugs 2011;71(1):43-64)*
G	An 8-wk OL study found no benefit of adding Li to Quet (vs Quet monotx) (Study 55 cited in *Ketter TA et al. J Affect Disord 2016;19:256-273*).
H	Acute responders to fluox randomized to Li monotx had no benefit vs PBO (*Amsterdam JD, Shults J. Am J Psychiatry 2010;167:792-800*)
I	Pts who were rolled over into a 52-wk OL study (amended to 26 weeks) from 3 RPCTs (see footnote Z) and received Brexpiprazole 0.5 to 3 mg/d (flexible dose) added to their current AD showed continued improvement (*Hobart M et al. J Clin Psychopharmacol 2019;39(3):203-209)*
J	In the network meta-analysis cited in footnote m, Val was sig'ly better than PBO in the prevention of manic but not dep relapse or recurrence. 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	Lam not better than PBO on the primary outcomes in any of 5 RPCTs, but meta-analysis yielded a sig, albeit modest, response rate (NNT=12). However, in more severely depressed pts (initial HRSD scores >24), NNT = 7 (*Geddes JR et al. Br J Psychiatry 2009;194:4-9*). Lam improves dep cognition and psychomotor slowing but not wt gain, sleep, energy, anxiety (*Mitchell et al. CNS Spectrums 2013;18:214-24*). In Lithium non-responders, **add-on** Lam was sig'ly more effective than add-on PBO (*van der Loos et al. J Clin Psychiatry 2009;70:223-31*).
L	See comprehensive review: *Bowden CL, Singh V. Lamotrigine for the tx of bipolar disorder. Expert Opin Pharmacother 2012;13(17):2565-71* Dosing should aim for 200 mg/d for the majority of patients. 50mg/d dose not better than PBO and 400mg/d dose not as good as 200 mg/d.
M	RPCT of manic or mixed episode pts who had remitted on oral Paliperidone, then 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	Three 6 week RPCTs: one was a +ve trial using Lurasidone as **monotherapy** in 20-60 mg/day and 80-120 mg/day dose ranges (Effect size = 0.51 for both ranges) [*Loebel A et al. Am J Psychiatry 2014;17(2):160-168*]; the other two trials used Lurasidone 20-120 mg/day **as adjunct to Li or Val** (one trial was +ve and one -ve; pooled results were +ve but with a small effect size of 0.25: *Tohen M et al. Bipolar Disord 2016;18:178*)
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** (with Li or Val) Lurasidone 20-80 mg/d found lower recurrence rates in the pts who had presented with an index episode of dep *(Calabrese J et al. Eur Psychiatry 2017;41;S209).* Also, in **OL** extension and continuation studies of the RPCTs cited in footnote N, pts continuing Lurasidone (modal dose = 60 mg/d) improved a further 5 points on the MADRS over the next 6 months (*Ketter T et al. Depress Anxiety 2016;33:424–434)* and then maintained improvement over the next 18 mo (*Pikalov A et al. Int J Bipolar Disord 2017;5:9*)
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 Health Canada-approved medications for acute bipolar depression are Quet (IR, XR), Lurasidone (monotx or with Li or Val) and Cariprazine
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	The only RPCT (*Young AH et al. J Clin Psychiatry 2010;71(2):150-162*) was –ve, but mean Li serum conc was only 0.61 mEq/l*).* Otherwise, only weak evidence for Li in acute tx of bipolar dep in old, very small crossover trials (*Bhagwagar Z, Goodwin GM. Clin Neurosci Res 2002;2:222-7*).
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 reports (n = 4) of benefit achieved by adding Lurasidone to AD and MS (*Nuñez NA, Gobbi G. Psychopharmacology 2017;37(2):263-4*)
Z	4 RPCTs (*Thase et al. J Clin Psychiatry 2015;76(9):1224-31* and *1232-40* respectively; *Hobart M et al. Curr Med Res Opin. 2018;34:633-642*; *Hobart M et al. J Clin Psychiatry 2018;79(4):17m12058*
α	3 RPCTs showed stat sig improvement for 1.5 mg/d dose and one for 3 mg/d dose; 1.5 mg/d dose had better functional improvement and tolerability *(Tohen M. Drug Des Devel Ther* 2021;15:2005-2012). A post hoc analysis found stat sig improvement of dep sx with both doses in dep mixed state pts, but only with the 1.5 mg/d dose in pts without concurrent manic sx (*McIntyre RS et al. CNS Spectr 2020;25(4):502–510*)