# NNT and NNH for Acute Bipolar Depression Monotherapy*

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| Pharmacotherapy | NNT | | NNH | | | | |
|---|---|---|---|---|---|---|---|
| | Response[a] | Remission[b] | Wt gain ≥7% | Sedation | Akathisia | Nausea | EPS |
| Quetiapine (IR/XR)[1] 300 or 600 mg/d | 6 | 6 | 15 | 2 | nr | nr | 19 |
| Lurasidone[2] 20 to 60 mg/d[c] | 4 | 6 | 29 | 77 | 18 | 37 | 40 |
| Lurasidone[2] 80 to 120 mg/d[d] | 5 | 7 | sp | 13 | 12 | 10 | 15 |
| OFC[3] 6/25, 6/50, or 12/50 mg/d[e] | 4 | 4 | 5 | 12 | nr | 36 | 15 |
| Olanzapine[3,4] 5 to 20 mg/d[f] | 11-12 | 11-12 | 5 | 6 | nr | bp | nr |
| Lithium[5] (mean median serum conc: .61 mEq/L)[g] | 15[h] | 13[h] | bp | 24 | nr | 12 | nr |
| Lamotrigine[6] 100 to 400 mg/d[i] | 12 | ? | nr | 37 | nr | bp | nr |
| Valproate[7] (mean serum conc: 430 - 568 µmol/L) | 7 | 7 | nr | nr | nr | 6 | nr |
| Aripiprazole[8] 5 to 30 mg/d[j] | 44[h] | bp | nr | 33 | 5 | 12 | nr |
| Cariprazine[9] 1.5 mg/d | 10 | 9 | 50 | 34 | 36 | 29 | 50 |
| Cariprazine[9] 3.0 mg/d | 9 | 13 | 50 | 50 | 13 | 21 | 25 |

*N.B. Based on calculations from placebo-controlled studies only. Important limitations to these indirect comparisons include the fact that the study populations (Bipolar I with or without Bipolar II, with or without psychosis) and the durations (usually 6 or 8 weeks) differed.

**In this table, NNT and NNH are rounded to the nearest whole number (i.e., rounded upwards only if ends in .5 or more).**

***Quetiapine, Lurasidone, and Cariprazine are approved by Health Canada for the treatment of bipolar I depression.***
***The U.S. FDA approves these three and the Olanzapine-Fluoxetine combination (OFC) for this indication.***

***Abbreviations:***

NNT = number of patients needed to treat to achieve one extra responder (or remitter) in the treatment arm compared to the placebo arm of the trial
NNH = number of patients needed to treat to harm (with that undesired effect) one extra person in the treatment arm compared to the placebo arm
OFC = olanzapine-fluoxetine combination
mg/d = milligrams per day
nr = incidence of the side effect was not reported because it was below a certain frequency (usually < 5% or 10%) in treatment and placebo groups
sp = same as placebo: incidence of undesirable effect was essentially identical in the treatment and placebo groups
bp = below placebo: the rate of remission (or the incidence of the undesirable effect) was less in the treatment group than in placebo group
RPCT = Randomized (double-blind) placebo-controlled trial

***Footnotes:***

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| a | Defined as 50% improvement on Montgomery-Asberg Depression Rating Scale (MADRS) in most studies |
| b | Defined as ≤ 12 points on MADRS at end point in most studies (≤ 10 points in Cariprazine studies) |
| c | Mean daily dose = 31.8 mg (taken with ≥ 350 calories) |
| d | Mean daily dose = 82.0 mg (taken with ≥ 350 calories) |
| e | 6/25 means olanzapine 6mg and fluoxetine 25 mg, etc. The mean daily doses were 7.4 mg/d for olanzapine and 39.3 mg/d for fluoxetine |
| f | The mean modal Olanzapine dose was 9.7 mg/d in Tohen M et al 2003[3] but not stated in Tohen M et al 2012[4] |
| g | 35% of patients had median serum concentrations below 0.6 mEq/L; so, this trial[5] may not represent a fair test of lithium for bipolar depression |
| h | The improvement was not statistically significant versus placebo |
| i | The 50 mg dose was subtherapeutic, so not included in the analyses. Most other patients in the trials[6] were titrated to a fixed dose of 200 mg/d |
| j | In both studies[8], aripiprazole was flexibly dosed and the most common dose at end point was 10 mg/d |

***References:***


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| 1 | NNT from reviews of 5 RPCTs: *Selle V et al Pharmacopsychiatry 2014;47:43-52* and *Chiesa A et al. Int Clin Psychopharmacol 2012;27(2):76-90*<br>NNH calculated from data provided in *Citrome L. CNS Spectrums 2014:19:1-12* (based on three 8-week RPCTs) |
| 2 | PREVAIL 2: a 6-week RPCT (*Loebel A et al. Am J Psychiatry 2014;17(2):160-168)* |
| 3 | 8-week RPCT of Olanzapine vs OFC vs placebo *(Tohen M et al. Arch Gen Psychiatry 2003;60(11):1079-88)* |
| 4 | 6-week RPCT of Olanzapine vs placebo *(Tohen M et al. Br J Psychiatry 2012;201:376-382)* |
| 5 | EMBOLDEN I: an 8-week RPCT of Lithium vs Quetiapine vs placebo *(Young AH et al. J Clin Psychiatry 2010;71(2):150-162)* |

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| 6 | NNT from an independent meta-analysis and meta-regression of individual patient data from 5 RPCTs with durations of 7 to 10 weeks. Although none of the individual trials reported a significant effect on the primary outcome, response rates with lamotrigine became statistically significant when data from the 5 trials were pooled. Although overall NNT = 12, in subgroup analyses response rate was significant only in those with severe (baseline HDRS > 24) depression (45.5% with Lam vs 30.1% with placebo, so NNT = 7; P = .001) but not in the less severely depressed subgroup (47.5% with Lam vs 44.6% with placebo, so NNT = 35; P = .4). *(Geddes JR et al. Br J Psychiatry 2009;194;4-9).* NNH values were calculated from data in *Calabrese JR et al. Bipolar Disorders 2008;10:323-333.* NNH for benign rash = 44. Serious rash: 1/1000 – 1/2000 |
| 7 | Meta-analysis of 4 small RPCTs: durations (6 or 8 weeks), patients included (bipolar I or both I and II) and definitions of response and remission varied in the trials, and total sample size was small, so the evidence was termed "preliminary" (*Bond DJ et al. J Affect Disord 2010;124:228-234)* |
| 8 | NNT and NNH calculated from data in *Thase ME et al. J Clin Psychopharmacol 2008;28(1):13-20* (2 identically designed, 8-week RPCTs) |
| 9 | Of 4 RPCTs (all with the primary endpoint of change from baseline to week 6 on the MADRS), one was failed, 3 were considered +ve and provided data on efficacy, showing stat sig improvement vs placebo with the 1.5 mg dose in all three, while the 3 mg dose was numerically superior in all three, but separated from placebo in only one (*Tohen M. Drug Des Devel Ther* 2021;15:2005-2012). A post hoc pooled data analysis found stat sig efficacy for both doses (*Yatham LN et al. Prim Care Companion CNS Disord. 2020;22(5):20m02611*). NNT for response and remission are from pooled analyses for each dose in these 3 studies *(Citrome L. Int J Clin Pract. 2019:73:13397);* NNH are from pooled analyses for each dose in all 4 studies *(Citrome L. et al. Psych Congress Virtual Meeting. September 10-13, 2020. Poster 112).* |