Supplementary Figure 1. Flow diagram of literature search

We searched Embase, PubMed, and the Cochrane Central Register of Controlled Trials for studies published prior to May 22, 2020. The search terms included: (bipolar disorder OR mania OR manic OR hypomania OR hypo-mania OR rapid cycle OR rapid-cycle OR bipolar depression OR affective) AND (randomized OR random OR randomly) AND (depot OR decanoate OR enanthate OR long acting injectable OR microsphere OR once monthly OR palmitate OR pamoate OR valproic acid OR valproate OR divalproate OR divalproex OR carbamazepine OR oxcarbazepine OR risperidone OR olanzapine OR aripiprazole OR quetiapine OR perospirone OR ziprasidone OR clozapine OR amisulpride OR asenapine OR blonanserin OR clothiapine OR iloperidone OR lurasidone OR mosapramine OR paliperidone OR remoxipride OR sertindole OR sulpiride OR tiapride OR chlorpromazine OR thioridazine OR mesoridazine OR loxapine OR molindone OR perphenazine OR thiothixene OR trifluoperazine OR haloperidol OR fluphenazine OR droperidol OR zuclopenthixol OR pimozide OR flupenthixol OR prochlorperazine OR lithium OR lamotrigine) AND (placebo). No language restriction was applied to the literature search. The authors assessed the retrieved reports against the inclusion and exclusion criteria and selected those that were eligible. In addition, the reference lists of the included articles and review articles were manually searched for additional relevant published and unpublished research, including conference abstracts. We also searched the clinical trial registries [ClinicalTrials.gov (http://clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/search/en/)] to ensure the set of RCTs was comprehensive and to minimize the influence of publication bias. Any discrepancies in selected articles were resolved by consensus in a meeting among the authors. Monotherapy and/or combination therapy studies of antidepressants with mood stabilizers or antipsychotics. Recent meta-analyses demonstrated that antidepressants might increase the risk of mood swings with no improvement in prophylaxis of new depressive episodes in patients with BD, and a previous NMA reported that lithium plus imipramine might increase relapse/recurrence of manic episodes in BD type I. Therefore, we excluded antidepressant studies from our meta-analysis.

1. Liu B, et al., Efficacy and safety of long-term antidepressant treatment for bipolar disorders - A meta-analysis of randomized controlled trials. J Affect Disord 2017; 223: 41-48.

2. Miura T, et al., Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry 2014; 1(5): 351-359.
Ahlfors, U. G., Baarstrup, P. C., Dencker, S. J., Elgen, K., Lingjaerde, O., Pedersen, V., Schou, M. & Aaskoven, O. (1981). Flupenthixol decanoate in recurrent manic-depressive illness. A comparison with lithium. Acta Psychiatr Scand 64, 226-37.

Altamura, A. C., Russo, M., Vismara, S. & Mundo, E. (2004). Comparative evaluation of olanzapine efficacy in the maintenance treatment of bipolar disorder. J Clin Psychopharmacol 24, 454-6.

Amsterdam, J. D., Lorenzo-Luaces, L., Soeller, I., Li, S. Q., Mao, J. J. & DeRubeis, R. J. (2015). Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar II depression: A randomized, double-blind, parallel-group, prospective study. J Affect Disord 185, 31-7.

Berk, M., Daglas, R., Dandash, O., Yucel, M., Henry, L., Hallam, K., Macneil, C., Hasty, M., Pantelis, C., Murphy, B. P., Kader, L., Damodaran, S., Wong, M. T. H., Conus, P., Ratheesh, A., McGorry, P. D. & Cotton, S. M. (2017). Quetiapine v. lithium in the maintenance phase following a first episode of mania: randomised controlled trial. Br J Psychiatry 210, 413-421.

Bobo, W. V., Epstein, R. A., Lynch, A., Patton, T. D., Bossaller, N. A. & Shelton, R. C. (2011). A randomized open comparison of long-acting injectable risperidone and treatment as usual for prevention of relapse, rehospitalization, and urgent care referral in community-treated patients with rapid cycling bipolar disorder. Clin Neuropharmacol 34, 224-33.

Brown, E., Dunner, D. L., McElroy, S. L., Keck, P. E., Adams, D. H., Degenhardt, E., Tohen, M. & Houston, J. P. (2009). Olanzapine/fluvoxetine combination vs. lamotrigine in the 6-month treatment of bipolar I depression. Int J Neuropsychopharmacol 12, 773-82.

Chengappa, K. N., Turkin, S. R., Schlicht, P. J., Murphy, S. L., Brar, J. S., Fagiolini, A., Houck, P. R., Garbutt, R. G. & Fredrick, N. (2010). A Pilot, 15-month, randomised effectiveness trial of Risperidone long-acting injection (RLAI) versus oral atypical antipsychotic agents (AAP) in persons with bipolar disorder. Acta Neuropsychiatr 22, 68-80.

Daglas, R., Cotton, S. M., Allott, K., Yucl, M., Macneil, C. A., Hasty, M. K., Murphy, B., Pantelis, C., Hallam, K. T., Henry, L. P., Conus, P., Ratheesh, A., Kader, L., Wong, M. T., McGorry, P. D. & Berk, M. (2016). A single-blind, randomised controlled trial on the effects of lithium and quetiapine monotherapy on the trajectory of cognitive functioning in first episode mania: A 12-month follow-up study. Eur Psychiatry 31, 20-8.

Gao, K., Goto, T., Yuan, C., Brownrigg, B., Conroy, C., Chan, P. K., Serrano, M. B., Ganoczy, S. J., Fang, F. & Calabrese, J. R. (2018). A Pilot Study of the Effectiveness of Lithium Versus Quetiapine Immediate Release Monotherapy in Patients With Bipolar Spectrum Disorders. J Clin Psychopharmacol 38, 422-434.

Goldberg, J. F., Bowden, C. L., Calabrese, J. R., Ketter, T. A., Dann, R. S., Frye, M. A., Suppes, T. & Post, R. M. (2008). Six-month prospective life charting of mood symptoms with lamotrigine monotherapy versus placebo in rapid cycling bipolar disorder. Biol Psychiatry 63, 125-30.

Greil, W., Ludwig-Mayerhofer, W., Erazo, N., Schochlin, C., Schmidt, S., Engel, R. R., Czernik, A., Giedke, H., Muller-Oerlinghausen, B., Osterheider, M., Rudolf, G. A., Sauer, H., Tegeler, J. & Wetterling, T. (1997). Lithium versus carbamazepine in the maintenance treatment of bipolar disorders—a randomised study. J Affect Disord 43, 151-61.

Juruena, M. F., Ottoni, G. L., Machado-Vieira, R., Carneiro, R. M., Wengarthner, N., Marquardt, A. R., Fleig, S. S., Broilo, L. & Busnello, E. A. (2009). Bipolar I and II disorder residual symptoms: oxcarbazepine and carbamazepine as add-on treatment to lithium in a double-blind, randomized trial. Prog Neuropsychopharmacol Biol Psychiatry 33, 94-9.

Kang, M. G., Qian, H., Keramatian, K., Chakrabarty, T., Saraf, G., Lam, R. W., Wong, H. & Yatham, L. N. (2020). Lithium vs valproate in the maintenance treatment of bipolar I disorder: A post-hoc analysis of a randomized double-blind placebo-controlled trial. Aust NZ J Psychiatry 54, 298-307.
Ketter, T. A., Houston, J. P., Adams, D. H., Risser, R. C., Meyers, A. L., Williamson, D. J. & Tohen, M. (2006). Differential efficacy of olanzapine and lithium in preventing manic or mixed recurrence in patients with bipolar I disorder based on number of previous manic or mixed episodes. J Clin Psychiatry 67, 95-101.

Licht, R. W., Nielsen, J. N., Gram, L. F., Vestergaard, P. & Bendz, H. (2010). Lamotrigine versus lithium as maintenance treatment in bipolar I disorder: an open, randomized effectiveness study mimicking clinical practice. The 6th trial of the Danish University Antidepressant Group (DUAG-6). Bipolar Disord 12, 483-93.

Maina, G., Albert, U., Rosso, G. & Bogetto, F. (2008). Olanzapine or lamotrigine addition to lithium in remitted bipolar disorder patients with anxiety disorder comorbidity: a randomized, single-blind, pilot study. J Clin Psychiatry 69, 609-16.

McIntyre, R. S., Cohen, M., Zhao, J., Alphas, L., Macek, T. A. & Panagides, J. (2010). Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. J Affect Disord 126, 358-65.

Nierenberg, A. A., McElroy, S. L., Friedman, E. S., Ketter, T. A., Shelton, R. C., Deckersbach, T., McInnis, M. G., Bowden, C. L., Tohen, M., Kocsis, J. H., Calabrese, J. R., Kinrys, G., Bobo, W. V., Singh, V., Kamali, M., Kemp, D., Brody, B., Reilly-Harrington, N. A., Sylvia, L. G., Shesler, L. W., Bernstein, E. E., Schoenfeld, D., Rabideau, D. J., Leon, A. C., Faraone, S. & Thase, M. E. (2016). Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. J Clin Psychiatry 77, 90-9.

Pae, C. U., Masand, P. S., Mandel, F. S. & O'Gorman, C. (2012). Achieving and sustaining remission in bipolar I disorder with ziprasidone: a post hoc analysis of a 24-week, double-blind, placebo-controlled study. Clin Drug Investig 32, 747-54.

Suppes, T., Marangell, L. B., Bernstein, I. H., Kelly, D. I., Fischer, E. G., Zboyan, H. A., Snow, D. E., Martinez, M., Al Jurdi, R., Shivakumar, G., Sureddi, S. & Gonzalez, R. (2008). A single blind comparison of lithium and lamotrigine for the treatment of bipolar II depression. J Affect Disord 111, 334-43.

Tohen, M., Ketter, T. A., Zarate, C. A., Suppes, T., Frye, M., Altshuler, L., Zajecka, J., Schuh, L. M., Risser, R. C., Brown, E. & Baker, R. W. (2003). Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. Am J Psychiatry 160, 1263-71.

Hand search for reference in the review article* (K = 3)

Cundall, R. L., Brooks, P. W. & Murray, L. G. (1972). A controlled evaluation of lithium prophylaxis in affective disorders. Psychol Med 2, 308-11.

Koyama, T., Higuchi, T., Yamawaki, S., Kanba, S., Terao, T. & Shinohara, A. (2011). Study SCA104779, an evaluation of BW430C (lamotrigine) versus placebo in the prevention of mood episodes in bipolar I disorder patients. Japanese Journal of Clinical Psychiatry 40, 369-383.

Melia, P. I. (1970). Prophylactic lithium: a double-blind trial in recurrent affective disorders. Br J Psychiatry 116, 621-4.

*Review article

Miura, T., Noma, H., Furukawa, T. A., Mitsuyasu, H., Tanaka, S., Stockton, S., Salanti, G., Motomura, K., Shimano-Katsuki, S., Leucht, S., Cipriani, A., Geddes, J. R. & Kanba, S. (2014). Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry 1, 351-9.
Studies included in the primary network meta-analysis (K = 32)

Amsterdam, J. D. & Shults, J. (2010). Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. Am J Psychiatry 167, 792-800.

Berwaerts, J., Melkote, R., Nuamah, I. & Lim, P. (2012). A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. J Affect Disord 138, 247-58.

Bowden, C. L., Calabrese, J. R., McElroy, S. L., Gyulai, L., Wassef, A., Petty, F., Pope, H. G., Jr., Chou, J. C., Keck, P. E., Jr., Rhodes, L. J., Swann, A. C., Hirschfeld, R. M. & Wozniak, P. J. (2000). A randomized, placebo-controlled 12-month trial of divalproex and lithium in maintenance treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. Arch Gen Psychiatry 57, 481-9.

Bowden, C. L., Calabrese, J. R., Sachs, G., Yatham, L. N., Asghar, S. A., Hompland, M., Montgomery, P., Earl, N., Smoot, T. M., DeVeaugh-Geiss, J. & Lamictal 606 Study, G. (2003). A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 60, 392-400.

Bowden CL, Singh V, Weisler R, Thompson P, Chang X, Quinones M, Mintz J. (2012). Lamotrigine vs. lamotrigine plus divalproex in randomized, placebo-controlled maintenance treatment for bipolar depression. Acta Psychiatr Scand. 126(5):342-50.

Calabrese, J. R., Bowden, C. L., Sachs, G., Yatham, L. N., Behnke, K., Mehtonen, O. P., Montgomery, P., Ascher, J., Paska, W., Earl, N., DeVeaugh-Geiss, J. & Lamictal 605 Study, G. (2003). A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 64, 1013-24.

Calabrese, J. R., Sanchez, R., Jin, N., Amatniek, J., Cox, K., Johnson, B., Perry, P., Hertel, P., Such, P., Salzman, P. M., McQuade, R. D., Nyilas, M. & Carson, W. H. (2017b). Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, 52-Week Randomized Withdrawal Study. J Clin Psychiatry 78, 324-331.

Calabrese, J. R., Shelton, M. D., Rapport, D. J., Youngstrom, E. A., Jackson, K., Bilali, S., Ganocy, S. J. & Findling, R. L. (2005). A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. Am J Psychiatry 162, 2152-61.

Calabrese, J. R., Suppes, T., Bowden, C. L., Sachs, G. S., Swann, A. C., McElroy, S. L., Kusumakar, V., Ascher, J. A., Earl, N. L., Greene, P. L. & Monaghan, E. T. (2000). A double-blind, placebo-controlled prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. J Clin Psychiatry 61, 841-50.

Carlson BX, Ketter TA, Sun W, Timko K, McQuade RD, Sanchez R, Vester-Blokland E, Marcus R. (2012). Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). Bipolar Disord. 14(1):41-53.

Coxhead, N., Silverstone, T & Cookson, J. (1992). Carbamazepine versus lithium in the prophylaxis of bipolar affective disorder. Acta Psychiatr Scand 85, 114-8.

Cundall, R. L., Brooks, P. W. & Murray, L. G. (1972). A controlled evaluation of lithium prophylaxis in affective disorders. Psychol Med 2, 308-11.

Dunner, D. L., Stallone, F. & Fieve, R. R. (1976). Lithium carbonate and affective disorders. V: A double-blind study of prophylaxis of depression in bipolar illness. Arch Gen Psychiatry 33, 117-20.

Fieve, R. R., Kumbhara, T. & Dunner, D. L. (1976). Lithium prophylaxis of depression in bipolar I, bipolar II, and unipolar patients. Am J Psychiatry 133, 925-9.

Geddes, J. R., Goodwin, G. M., Rendell, J., Azorin, J. M., Cipriani, A., Ostacher, M. J., Morriss, R., Alder, N. & Juszczak, E. (2010). Lithium plus valproate combination therapy versus...
monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 375, 385-95.

Hartong, E. G., Moleman, P., Hoogduin, C. A., Broekman, T. G., Nolen, W. A. & LitCar, G. (2003). Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. J Clin Psychiatry 64, 144-51.

Kane, J. M., Quitkin, F. M., Rifkin, A., Ramos-Lorenzi, J. R., Nayak, D. D. & Howard, A. (1982). Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison. Arch Gen Psychiatry 39, 1065-9.

Keck, P. E., Jr., Calabrese, J. R., McIntyre, R. S., McQuade, R. D., Carson, W. H., Eudicone, J. M., Carlson, B. X., Marcus, R. N., Sanchez, R. & Aripiprazole Study, G. (2007). Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 68, 1480-91.

Kleindienst, N. & Greil, W. (2000). Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. Neuropsychobiology 42 Suppl 1, 2-10.

Koyama, T., Higuchi, T., Yamawaki, S., Kanba, S., Terao, T. & Shinohara, A. (2011). Study SCA104779, an evaluation of BW430C (lamotrigine) versus placebo in the prevention of mood episodes in bipolar I disorder patients. Japanese Journal of Clinical Psychiatry 40, 369-383.

Melia, P. I. (1970). Prophylactic lithium: a double-blind trial in recurrent affective disorders. Br J Psychiatry 116, 621-4.

Prien, R. F., Klett, C. J. & Caffey, E. M., Jr. (1973a). Lithium carbonate and imipramine in prevention of affective episodes. A comparison in recurrent affective illness. Arch Gen Psychiatry 29, 420-5.

Prien, R. F., Caffey, E. M., Jr. & Klett, C. J. (1973b). Prophylactic efficacy of lithium carbonate in manic-depressive illness. Report of the Veterans Administration and National Institute of Mental Health collaborative study group. Arch Gen Psychiatry 28, 337-41.

Quiroz, J. A., Yatham, L. N., Palumbo, J. M., Karcher, K., Kushner, S. & Kusumakar, V. (2010). Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. Biol Psychiatry 68, 156-62.

Szegedi, A., Durgam, S., Mackle, M., Yu, S. Y., Wu, X., Mathews, M. & Landbloom, R. P. (2018). Randomized, Double-Blind, Placebo-Controlled Trial of Asenapine Maintenance Therapy in Adults With an Acute Manic or Mixed Episode Associated With Bipolar I Disorder. Am J Psychiatry 175, 71-79.

Tohen, M., Calabrese, J. R., Sachs, G. S., Banov, M. D., Detke, H. C., Risser, R., Baker, R. W., Chou, J. C. & Bowden, C. L. (2006). Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry 163, 247-56.

Tohen, M., Greil, W., Calabrese, J. R., Sachs, G. S., Yatham, L. N., Oerlinghausen, B. M., Koukopoulos, A., Cassano, G. B., Grunze, H., Licht, R. W., Dell'Osso, L., Evans, A. R., Risser, R., Baker, R. W., Crane, H., Dossenbach, M. R. & Bowden, C. L. (2005). Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 162, 1281-90.

Vieta, E., Cruz, N., Garcia-Campayo, J., de Arce, R., Manuel Crespo, J., Valles, V., Perez-Blanco, J., Roca, E., Manuel Olivares, J., Morinigo, A., Fernandez-Villamor, R. & Comes, M. (2008a). A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. Int J Neuropsychopharmacol 11, 445-52.

Vieta, E., Montgomery, S., Sulaiman, A. H., Cordoba, R., Huberlant, B., Martinez, L. & Schreiner, A. (2012). A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. Eur Neuropsychopharmacol 22, 825-35.
Weisler, R. H., Nolen, W. A., Neijber, A., Hellqvist, A., Paulsson, B. & Trial 144 Study, I. (2011). Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). J Clin Psychiatry 72, 1452-64.

Woo, Y. S., Bahk, W. M., Chung, M. Y., Kim, D. H., Yoon, B. H., Lee, J. H., Ahn, Y. M., Chung, S. K., Kim, J. G., Lee, K. H. & Paik, K. C. (2011). Aripiprazole plus divalproex for recently manic or mixed patients with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind maintenance trial. Hum Psychopharmacol 26, 543-53.

Young, A. H., McElroy, S. L., Olusson, B., Paulsson, B., Embolen, I. & Embolen, I. I. I. (2014). A randomised, placebo-controlled 52-week trial of continued quetiapine treatment in recently depressed patients with bipolar I and bipolar II disorder. World J Biol Psychiatry 15, 96-112.

Studies included in the secondary network meta-analysis (K = 6)

Bowden, C. L., Vieta, E., Ice, K. S., Schwartz, J. H., Wang, P. P. & Versavel, M. (2010). Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. J Clin Psychiatry 71, 130-7.

Calabrese, J. R., Pikalov, A., Streicher, C., Cucchiaro, J., Mao, Y. & Loebel, A. (2017a). Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder. Eur Neuropsychopharmacol 27, 865-876.

Marcus, R., Khan, A., Rollin, L., Morris, B., Timko, K., Carson, W. & Sanchez, R. (2011). Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. Bipolar Disord 13, 133-44.

Suppes, T., Vieta, E., Liu, S., Brecher, M., Paulsson, B. & Trial, I. (2009). Maintenance treatment for patients with bipolar I disorder: results from a north american study of quetiapine in combination with lithium or divalproex (trial 127). Am J Psychiatry 166, 476-88.

Tohen, M., Chengappa, K. N., Suppes, T., Baker, R. W., Zarate, C. A., Bowden, C. L., Sachs, G. S., Kupfer, D. J., Ghaemi, S. N., Feldman, P. D., Risser, R. C., Evans, A. R. & Calabrese, J. R. (2004). Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. Br J Psychiatry 184, 337-45.

Vieta, E., Suppes, T., Eggens, I., Persson, I., Paulsson, B. & Brecher, M. (2008). Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). J Affect Disord 109, 251-63.

Studies that were not included in the network meta-analysis (K = 3)

Macfadden, W., Alphs, L., Haskins, J. T., Turner, N., Turkoz, I., Bossie, C., Kuja, M. & Mahmoud, R. (2009). A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. Bipolar Disord 11, 827-39.

Yatham, L. N., Fallu, A. & Binder, C. E. (2007). A 6-month randomized open-label comparison of continuation of oral atypical antipsychotic therapy or switch to long acting injectable risperidone in patients with bipolar disorder. Acta Psychiatr Scand Suppl, 50-6.

Zarate, C. A., Jr. & Tohen, M. (2004). Double-blind comparison of the continued use of antipsychotic treatment versus its discontinuation in remitted manic patients. Am J Psychiatry 161, 169-71.
### Supplementary Figure 2. Risk of bias summary

| Study          | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) |Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|----------------|---------------------------------------------|----------------------------------------|----------------------------------------------------------|-------------------------------------------------|----------------------------------------|-------------------------------------|------------|
| Araki 2017     | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Kane 2012      | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Hallgren 2003  | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Geiger 2003    | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Ye 2003        | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Kim 2012       | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Ye 2008a       | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Torer 2005     | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Serger 2004    | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Plessen 1973   | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Mull 1973      | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| MacFarland 2009| ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |
| Koyama 2011    | ![Green](Image)                              | ![Green](Image)                         | ![Green](Image)                                          | ![Green](Image)                                 | ![Green](Image)                         | ![Green](Image)                       |            |

Other bias: insufficient assessment of recurrent of mood episode
**Supplementary Table 1. Study characteristics**

**Supplementary Table 1-1. Monotherapy studies**

| Study name, study duration, sponsor | Diagnosis (%BDII, criteria), mood status at recruitment | %female, mean age | %rapid cycling | Pre-randomization treatment | Double-blind treatment (n)* | Definition of relapse |
|-----------------------------------|------------------------------------------------------|-----------------|--------------|-----------------------------|---------------------------|----------------------|
| **Amsterdam 2010**, 50 wk, AC     | BDII (100%, DSM-IV-TR), DE                           | 46.3%, 38.0 yr  | ni           | FLU 20-80 mg/d              | (1) LIT 0.5-1.5 mmol/L (26) | (1) MDE in DSM-IV-TR and HAMD ≥ 14 |
|                                   |                                                      |                 |              |                             |                           | (2) HME in DSM-IV-TR (symptoms ≥ 4 and ≥4d) and YMRS ≥ 12 |
| **Berwaerts 2012**, 171.4 wk, IN  | BDI (0%, DSM-IV), MaE or MiE                         | 53.4%, 40.0 yr  | 0%          | PAL 3-12 mg/d               | (1) PAL 3-12 mg/d (152)   | (1) YMRS ≥ 15 and CGI-BP-S for mania ≥ 4 |
|                                   |                                                      |                 |              |                             |                           | (2) YMRS < 15 and MADRS ≥ 16 and CGI-BP-S for depression ≥ 4 |
|                                   |                                                      |                 |              |                             |                           | (3) Hospitalization |
|                                   |                                                      |                 |              |                             |                           | (4) Additional therapeutic intervention |
| **Bowden 2000**, 52 wk, IN        | BDI (0%, DSM-III-R), MaE, MiE or EU                  | 50.9%, 39.2 yr  | ni           | LIT or DIV                  | (1) DIV 71-125 μg/mL (187) | (1) Depression : Additional AD intervention or discontinuation because of symptoms |
|                                   |                                                      |                 |              |                             |                           | (2) LIT 0.8-1.2 mmol/L (91) |
|                                   |                                                      |                 |              |                             |                           | (3) PLA (94) |
| **Bowden 2003**, 76 wk, IN        | BDI (0%, DSM-IV), MaE or HME                         | 52.8%, 41.1 yr  | ni           | LAM 100-200 mg/d            | (1) LAM 100-400 mg/d (59)  | (1) Additional therapeutic intervention including ECT |
|                                   |                                                      |                 |              |                             |                           | (2) LIT 0.8-1.1 mEq/L (47) |
|                                   |                                                      |                 |              |                             |                           | (3) PLA (70) |
| **Calabrese 2000**, 26 wk, IN     | BDI or II (28.9%, DSM-IV), MaE, HME, MiE, DE or EU  | 57.2%, 38.0 yr  | 100%         | LAM 100-200 mg/d            | (1) LAM 100-500 mg/d (93)  | (1) Additional pharmacological intervention |
|                                   |                                                      |                 |              |                             |                           | (2) PLA (89) |
| **Calabrese 2003**, 76 wk, IN     | BDI (0%, DSM-IV), DE                                | 54.9%, 43.4 yr  | ni           | LAM ≥ 100 mg/d              | (1) LAM 200-400 mg/d (171) | (1) Additional therapeutic intervention including ECT |
|                                   |                                                      |                 |              |                             |                           | (2) LIT 0.8-1.1 mEq/L (121) |
|                                   |                                                      |                 |              |                             |                           | (3) PLA (121) |
| Study name, study duration, sponsor | Diagnosis (%BDII, criteria), mood status at recruitment | %female, mean age | %rapid cycling | Pre-randomization treatment | Double-blind treatment (n)* | Definition of relapse |
|-------------------------------------|------------------------------------------------------|-----------------|---------------|-----------------------------|----------------------------|---------------------|
| Calabrese 2005*, 80 wk, AC          | BDI or II (60.0%, DSM-IV), MaE, HME, MiE, DE or EU   | 51.7%, 37.1 yr  | 100%          | DIV ≥ 50 μg/ml + LIT ≥ 0.8 mEq/l | (1) DIV ≥50 μg/mL (28)   | (1) HAMD24 ≥ 20 for 8 wk |
| Calabrese 2017b, 52 wk, IN          | BDI (0%, DSM-IV-TR), MaE or MiE                      | 57.5%, 40.6%    | 0%            | AOM 400 mg/4w               | (1) AOM 400 mg/4w (133)  | (1) YMRS ≥ 15       |
| Coxhead 1992*, 52 wk, IN            | BD (ni, DSM-III), EU                                | 67.7%, 48.0 yr  | ni            | LIT                         | (1) CAR 38-51 mmol/L (15) | (1) Author defined |
| Cundall 1972*, 26 wk, AC            | Manic-Depressive (ni, ni), ni                       | 61.5%, 53.7 yr  | ni            | LIT                         | (1) LIT 0.5-1.2 mEq/L (8) | (1) diagnosed clinically |
| Dunner 1976*, 65 wk, AC             | BDII, BD others (100%, Feighner), EU                 | 57.5%, 51.2 yr  | 15.0%         | ni                          | (1) LIT 0.8-1.2 mEq/L (16) | (1) Additional pharmacological intervention |
| Fieve 1976*, 64 (mean) wk, AC       | BDI or II (34.0%, Feighner), EU                      | 50.9%, 46.6     | 3.8%          | ni                          | (1) LIT 0.7-1.3 mEq/L (24) | (1) Author defined |
| Geddes 2010*, 104 wk, AC            | BDI (0%, DSM-IV), EU                                | 48.6%, 43.5 yr  | ni            | LIT 0.4-1.0 mEq/l + VAL ≥ 750 mg/d | (1) LIT 0.4-1.0 mEq/L (110) | (1) Hospitalization |
|                                    |                                                      |                 |               |                             | (2) VAL 750-1250 mg/d (110) | (2) Additional therapeutic intervention |
|                                    |                                                      |                 |               |                             | (3) LIT + VAL (110)       |                     |
| Study name, study duration, sponsor | Diagnosis (%BDII, criteria), mood status at recruitment | %female, mean age | %rapid cycling | Pre-randomization treatment | Double-blind treatment (n)* | Definition of relapse |
|------------------------------------|--------------------------------------------------------|------------------|--------------|-----------------------------|-----------------------------|----------------------|
| Hartong 2003*, 104 wk, IN          | BDI or II (ni, DSM-III-R), EU                          | 54.3%, 41.9 yr   | ni           | < 6 m use CAR or LIT        | (1) CAR 6-10 mg/L (30)      | (1) DE in DSM-IV      |
|                                    |                                                        |                  |              |                             | (2) LIT 0.6-1.0 mmol/L (23) | (2) MaE/HME in DSM-IV   |
| Kane 1982*, 104 wk, AC             | BDII (100%, RDC), EU                                   | 69.4%, 47.5 yr   | ni           | IMI 150 mg/d                | (1) LIT 0.8-1.2 mEq/L (4)   | (1) Major depression for a wk (RDC) |
|                                    |                                                        |                  |              |                             | (2) PLA (7)                 | (2) Mania for a wk (RDC) |
|                                    |                                                        |                  |              |                             |                            | (3) Minor depression for 4 wks (RDC) |
|                                    |                                                        |                  |              |                             |                            | (4) Hypomania for 4 wks (RDC) |
| Keck 2007*, 100 wk, IN             | BDI (0%, DSM-IV), MaE or MiE                           | 67.1%, 39.7 yr   | 17.5%        | ARI 15-30 mg/d              | (1) ARI 15-30 mg/d (78)     | (1) Hospitalization    |
|                                    |                                                        |                  |              |                             | (2) PLA (83)                | (2) Additional therapeutic intervention |
|                                    |                                                        |                  |              |                             |                            | (3) Discontinuation due to lack of efficacy |
|                                    |                                                        |                  |              |                             |                            | (4) Sufficient severity to admission to hospital |
|                                    |                                                        |                  |              |                             |                            | (5) Additional pharmacological intervention |
|                                    |                                                        |                  |              |                             |                            | (6) Hospitalization      |
|                                    |                                                        |                  |              |                             |                            | (7) Sufficient severity to admission to hospital |
|                                    |                                                        |                  |              |                             |                            | (8) Hospitalization      |
|                                    |                                                        |                  |              |                             |                            | (9) Sufficient severity to admission to hospital |
|                                    |                                                        |                  |              |                             |                            | (10) Hospitalization     |
|                                    |                                                        |                  |              |                             |                            | (11) Hospitalization     |
|                                    |                                                        |                  |              |                             |                            | (12) Hospitalization     |
| Koyama 2011*, 26 wk, IN            | BDI (0%, DSM-IV-TR), MaE, MiE, DE or EU               | 56.3%, 42.8 yr   | ni           | LAM 100-200 mg/d            | (1) LAM 100-200 mg/d (45)   | (1) Additional pharmacological intervention |
|                                    |                                                        |                  |              |                             | (2) PLA (58)                | (2) Hospitalization      |
| Melia 1970*, 104 wk, IN            | BD (ni, ICD-9), EU                                     | 90.9%, 51.5 yr   | ni           | LIT                         | (1) LIT 500-1500 mg/d (5)    | (1) Sufficient severity to admission to hospital |
|                                    |                                                        |                  |              |                             | (2) PLA (6)                 | (2) Hospitalization      |
| Prien 1973a*, 17.3 wk, AC          | BD (ni, ni), DE                                       | 23.0%, 45.7 yr   | ni           | LIT or IMI                  | (1) LIT 0.5-1.4 mEq/L (18)   | (1) Additional pharmacological intervention |
|                                    |                                                        |                  |              |                             | (2) PLA (13)                | (2) Hospitalization      |
| Prien 1973b*, 104 wk, AC           | Manic-depressive manic type (ni, ni), MaE or HME      | 35.1%, 44 (median) yr | ni | LIT                         | (1) LIT 0.5-1.4 mEq/L (101) | (1) Additional pharmacological intervention |
|                                    |                                                        |                  |              |                             | (2) PLA (104)               | (2) Hospitalization      |
| Study name, study duration, sponsor | Diagnosis (%BDII, criteria), mood status at recruitment | %female, mean age | %rapid cycling | Pre-randomization treatment | Double-blind treatment (n)* | Definition of relapse |
|-------------------------------------|----------------------------------------------------------|------------------|---------------|---------------------------|--------------------------|---------------------|
| Quiroz 2010*, 104 wk, IN            | BDI (0%, DSM-IV-TR), MaE, MiE or EU                     | 48.5%, 39.0 yr   | 0%            | RIS-LAI 12.5, 25, 37.5, 50 mg/2wk | (1) RIS-LAI 12.5-50 mg/2wk (154) (2) PLA (149) | (1) YMRS > 12 (2) MADRS > 12 (3) CGI-S > 4 (3) Hospitalization (4) Additional therapeutic intervention including increase dosage of RIS (5) Any mood episode in DSM-IV |
| Szegedi 2018, 26 wk, IN             | BDI (0%, DSM-IV-TR), MaE or MiE                        | 54.8%, 41.9 yr   | 0%            | ASE 5 or 10 mg bid         | (1) ASE 10-20 mg (126) (2) PLA (127) | (1) YMRS ≥ 16 (2) MADRS ≥ 16 (3) Hospitalization (4) Additional therapeutic intervention (5) Discontinuation because of a mood event |
| Tohen 2005*, 48 wk, IN              | BDI (0%, DSM-IV), MaE or MiE                           | 52.9%, 42.4 yr   | 3%            | LIT 0.6-1.2 mEq/l + OLA 5-20 mg/d | (1) LIT 0.6-1.2 mEq/L (214) (2) OLA 5-20 mg/d (217) | (1) HAMD ≥ 15 (2) YMRS ≥ 15 |
| Tohen 2006*, 48 wk, IN              | BDI (0%, DSM-IV), MaE or MiE                           | 61.2%, 40.6 yr   | 49.6%         | OLA 5-20 mg/d              | (1) OLA 5-20 mg/d (225) (2) PLA (136) | (1) HAMD ≥ 15 (2) YMRS ≥ 15 (3) Hospitalization |
| Vieta 2012*, 78 wk, IN              | BDI (0%, DSM-IV-TR), MaE, MiE or EU                    | 52.1%, 36.9 yr   | 0%            | RIS-LAI 25, 37.5, 50 mg/2wk | (1) OLA 10 mg/d (131) (2) RIS-LAI 25-50 mg/2wk (132) (3) PLA (135) | (1) YMRS > 12 (2) MADRS > 12 (3) CGI-S ≥ 4 (3) Hospitalization (4) Additional therapeutic intervention including increase dosage of RIS |
| Study name, study duration, sponsor | Diagnosis (%BDII, criteria), mood status at recruitment | %female, mean age | %rapid cycling | Pre-randomization treatment | Double-blind treatment (n)* | Definition of relapse |
|-----------------------------------|----------------------------------------------------------|------------------|---------------|-----------------------------|-----------------------------|-----------------------|
| Weisler 2011*, 104 wk, IN          | BDI (0%, DSM-IV), MaE, MiE, DE or EU                     | 51.5%, 39.5 yr   | 13.4%         | QUE 300-800 mg/d            | (1) LIT 0.6-1.2 mEq/L (364) | (1) YMRS ≥ 20 |
|                                   |                                                          |                  |               | (2) QUE 300-800 mg/d (404)  | (2) MADRS ≥ 20            | (2) MADRS ≥ 20 |
|                                   |                                                          |                  |               | (3) PLA (404)               | (3) Additional pharmacological intervention | (3) Hospitalization |
|                                   |                                                          |                  |               |                             | (4) Additional therapeutic intervention | (4) Hospitalization |
|                                   |                                                          |                  |               |                             | (5) Discontinuation because of a mood event | (5) Discontinuation because of a mood event |
| Young 2014*, 52 wk, IN             | BDI or II (39.6%, DSM-IV), DE                           | 59.6%, 40.1 yr   | 8.7%          | QUE 300 or 600 mg/d         | (1) QUE 300-600 mg/d (291) | (1) YMRS ≥ 16 |
|                                   |                                                          |                  |               | (2) PLA (294)               | (2) MADRS ≥ 20            | (2) MADRS ≥ 20 |
|                                   |                                                          |                  |               |                             | (3) Hospitalization       | (3) Hospitalization |
|                                   |                                                          |                  |               |                             | (4) Additional therapeutic intervention | (4) Hospitalization |
|                                   |                                                          |                  |               |                             | (5) Discontinuation because of a mood event | (5) Discontinuation because of a mood event |
## Supplementary Table 1-2. Combination therapy studies

| Study name, study duration, sponsor | Diagnosis (%BDII, criteria), mood status at recruitment | %female, mean age | %rapid cycling | Pre-randomization treatment | Double-blind treatment (n)* | Definition of relapse |
|-------------------------------------|----------------------------------------------------------|------------------|---------------|-----------------------------|-----------------------------|----------------------|
| Bowden 2010, 24 wk, IN              | BDI (0%, DSM-IV), MaE or MiE                             | 53.8%, 38.8 yr   | ni            | ZIP 80-160 mg/d + LIT 0.6-1.2 mEq/L or VAL 50-125 μg/ml | (1) ZIP 80-160 mg/d + LIT 0.6-1.2 mEq/L or VAL 50-125 μg/ml (127) | (1) Additional therapeutic intervention |
|                                    |                                                          |                  |               |                             | (2) PLA + LIT 0.6-1.2 mEq/L or VAL 50-125 μg/ml (113)     |                      |
| Bowden 2012*, 34.7 wk, AC           | BDI or II (21.0%, DSM-IV), DE or EU                     | 57.4%, 40.7 yr   | ni            | LAM 50-200 mg/d + DIV 45-120 μg/ml | (1) LAM 50-200 mg/d + DIV 500-2500 mg/d (41) | (1) MRS ≥ 15 |
|                                    |                                                          |                  |               |                             | (2) PLA + LAM 50-200 mg/d (45)                         | (2) MADRS ≥ 15      |
| Calabrese 2017a, 28 wk, IN          | BDI (0%, DSM-IV-TR), MaE, MiE or DE                      | 56.3%, 44.5 yr   | 13.3%         | LUR 20-80mg/d + LIT 0.4-1.2 mEq/l or VAL 50-125 μg/ml  | (1) LUR 20-80mg/d + LIT 0.4-1.2 mEq/L or VAL 50-125 μg/ml (246) | (1) YMRS ≥ 18 |
|                                    |                                                          |                  |               |                             | (2) PLA + LIT 0.4-1.2mEq/L or VAL 50-125 μg/mL (250)    | (2) MADRS ≥ 18      |
|                                    |                                                          |                  |               |                             |                                                                 | (3) CGI-BP-S ≥ 4    |
|                                    |                                                          |                  |               |                             |                                                                 | (4) Hospitalization |
|                                    |                                                          |                  |               |                             |                                                                 | (5) Any mood episode in DSM-IV-TR |
|                                    |                                                          |                  |               |                             |                                                                 | (6) Discontinuation because of a mood event |
| Carlson 2012*, 52 wk, IN            | BDI (0%, DSM-IV-TR), MaE or MiE                         | 65.0%, 39.1 yr   | 27.1%         | ARI 10-30 mg/d + LAM 100-200 mg/d | (1) ARI 10-30 mg/d + LAM 100-200 mg/d (178) | (1) Hospitalization |
|                                    |                                                          |                  |               |                             | (2) PLA + LAM100-200 mg/d (173)                          | (2) SAE or worsening disease (and YMRS > 14 and/or MADRS > 16) |
|                                    |                                                          |                  |               |                             |                                                                 | (3) Discontinuation due to lack of efficacy (and YMRS > 14 and/or MADRS > 16) |
| Study name, study duration, sponsor | Diagnosis (%BDII, criteria), mood status at recruitment | %female, mean age | %rapid cycling | Pre-randomization treatment | Double-blind treatment (n)* | Definition of relapse |
|-----------------------------------|---------------------------------|-----------------|---------------|-----------------------------|----------------------------|----------------------|
| Macfadden 2009, 52 wk, IN         | BDI (0%, DSM-IV-TR), MaE, HME, MiE, DE or EU | 28.2%. 38.9 yr | 100%          | TAU                        | (1) RISLAI 25-50 mg/d + TAU (65)  
(2) TAU (59) | (1) YMRS > 15 and CGI-BP-S ≥ 4, CGI-BP-C ≥ 6 or GAF decrease >10  
(2) MADRS > 16 and CGI-BP-S ≥ 4, CGI-BP-C ≥ 6 or GAF decrease >10  
(3) Hospitalization [(1) or (2)]  
(4) Hospitalization (ISST > 7) |
| Marcus 2011, 52 wk, IN            | BDI (0%, DSM-IV-TR), MaE or MiE | 54.9%, 39.0 yr | 3.9%          | ARI 10-30 mg/d + LIT 0.6-1.0 mmol/L or VAL 50-125 μg/ml | (1) ARI 10-30 mg/d + LIT 0.6-1.0 mmol/L or VAL 50-125 μg/ml (168)  
(2) PLA + LIT 0.6-1.0 mmol/L or VAL 50-125 μg/ml (169) | (1) Hospitalization  
(2) SAE of worsening disease (and YMRS > 16 and/or MADRS > 16)  
(3) Discontinuation due to lack of efficacy (and YMRS > 16 and/or MADRS > 16) |
| Suppes 2009, 104 wk, IN           | BDI (0%, DSM-IV), MaE, MiE or DE | 52.5%, 40.1 yr | 51.0%         | QUE 400-800 mg/d + DIV 50-125 μg/mL or LIT 0.5-1.2 mEq/l | (1) QUE 400-800 mg/d + DIV 50-125 μg/mL or LIT 0.5-1.2 mEq/l (310)  
(2) PLA + DIV 50-125 μg/mL or LIT 0.5-1.2 mEq/l (313) | (1) YMRS ≥ 20  
(2) MADRS ≥ 20  
(3) Hospitalization  
(4) Additional therapeutic intervention  
(5) Discontinuation because of a mood event |
| Tohen 2004, 78 wk, IN             | BDI (0%, DSM-IV), MaE or MiE | 51.5%, 41.3 yr | 41.4%         | OLA 5-20 mg/d + LIT 0.6-1.2 mmol/L or VAL 50-125 μg/ml | (1) OLA 5-20 mg/d + LIT 0.6-1.2 mmol/L or VAL 50-125 μg/ml (51)  
(2) PLA + LIT 0.6-1.2 mmol/L or VAL 50-125 μg/mL (48) | (1) HAMD ≥ 15  
(2) YMRS ≥ 15  
(3) Any mood episode in DSM-IV |
| Study name, study duration, sponsor | Diagnosis (%BDII, criteria), mood status at recruitment | %female, mean age | %rapid cycling | Pre-randomization treatment | Double-blind treatment (n)* | Definition of relapse |
|----------------------------------|------------------------------------------------|-----------------|--------------|-----------------------------|---------------------------|-----------------------|
| Vieta 2008a*, 52 wk, IN          | BDI or II (23.6%, DSM-IV-TR), EU              | 65.5%, 43.5 yr  | ni           | LIT ≥ 0.6 mEq/l             | (1) OXC 300-1200 mg/d + LIT ≥ 0.6 mEq/L (26) | (1) YMRS > 12 |
|                                 |                                                |                 |              |                             | (2) PLA + LIT ≥ 0.6 mEq/L (29) | (2) MADRS > 20 |
| Vieta 2008b, 104 wk, IN          | BDI (0%, DSM-IV), MaE, MiE or DE              | 55.0%, 42.1 yr  | 23.9%        | QUE 400-800 mg/d + DIV 50-125 μg/ml or LIT 0.5-1.2 mEq/l | (1) QUE 400-800 mg/d + DIV 50-125 μg/mL or LIT 0.5-1.2 mEq/l (336) | (1) YMRS ≥ 20 |
|                                 |                                                |                 |              |                             | (2) PLA + DIV 50-125 μg/mL or LIT 0.5-1.2 mEq/l (367) | (2) MADRS ≥ 20 |
|                                 |                                                |                 |              |                             |                            | (3) Hospitalization |
|                                 |                                                |                 |              |                             |                            | (4) Additional therapeutic intervention |
|                                 |                                                |                 |              |                             |                            | (5) Discontinuation because of a mood event |
| Woo 2011*, 24 wk, IN             | BDI (0%, DSM-IV), MaE or MiE                  | 61.4%, 38.3 yr  | ni           | ARI 10-30 mg/d + DIV 50-120 μg/ml | (1) ARI 10-30 mg/d + DIV 50-120 μg/mL (40) | (1) YMRS ≥ 15 |
|                                 |                                                |                 |              |                             | (2) PLA + DIV 50-120 μg/mL (43) | (2) MADRS ≥ 16 |
|                                 |                                                |                 |              |                             |                            | (3) Hospitalization |
|                                 |                                                |                 |              |                             |                            | (4) Additional therapeutic intervention |
| Yatham 2007, 26 wk, IN           | BDI or II (34.7%, DSM-IV-TR), ni              | 51.0%, 40.9 yr  | ni           | OLA, QUE or RIS in combination with a maximum of two of LAM, LIT, or VAL | (1) RISLAI 25-50 mg/d (23) | (1) Any mood episode in DSM-IV |
|                                 |                                                |                 |              |                             | (2) OLA mean 8 mg/d, QUE mean 352.3 mg/d or RIS mean 1.4 mg/d (26) | (2) Any mood episode in DSM-IV |
|                                 |                                                |                 |              |                             | Patients who had taken LAM, LIT, or VAL continue them | |
| Zarate 2004, 26 wk, AC           | BD (ni, DSM-IV), MaE or MiE                   | 78.9%, 35.8 yr  | 0%           | PER 4-64 mg/d + CAR 4-12 mg/l, LIT 0.6-1.2 mEq/l or VAL 50-125 mg/l | (1) PER 4-64 mg/d + CAR 4-12 mg/L, LIT 0.6-1.2 mEq/L or VAL 50-125 mg/L (18) | (1) Any mood episode in DSM-IV |
|                                 |                                                |                 |              |                             | (2) PLA + CAR 4-12 mg/L, LIT 0.6-1.2 mEq/L or VAL 50-125 mg/L (19) | (2) Any mood episode in DSM-IV |

*This study was included in the previous meta-analysis (Miura et al., 2014).
**The study with enrichment design was underlined.

The following studies were included in the previous meta-analysis (Miura et al., 2014), but not our study because the studies did not have multiple treatment arms other than antidepressants.

Amsterdam JD, Shults J. Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study. Int Clin Psychopharmacol. 2005 Sep;20(5):257-64.

Kane JM, Quitkin FM, Rifkin A, Ramos-Lorenzi JR, Saraf K, Howard A, Klein DF. Prophylactic lithium with and without imipramine for bipolar I patients: a double-blind study [proceedings]. Psychopharmacol Bull. 1981 Jan;17(1):144-5.

Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry. 1984 Nov;41(11):1096-104.

AC: academia, AD: antidepressant, AOM: aripiprazole once-monthly, AP: antipsychotic, ARI: aripiprazole, ASE: asenapine, BD: bipolar disorder, CAR: carbamazepine, CGI-BP-S(C): Clinical Global Impressions of Bipolar Disorder-Severity(-Change), d: day, DIV: divalproex, DSM: Diagnostic and Statistical Manual of Mental Disorders, ECT: electroconvulsive therapy, EU: euthymia, FLU: fluoxetine, GAF: Global Assessment of Functioning, HAMD: Hamilton Rating Scale for Depression, HME: hypomanic episode, ICD: International Classification of Diseases, IMI: imipramine, IN: industry, ISST: InterSePT Scale for Suicidal Thinking, LAM: lamotrigine, LIT: lithium, MaE: manic episode/(M)DE: (major) depressive episode, MiE: mixed episode, MRS: Mania Rating Scale, n: number of patients, ni: not information, NOS: not otherwise specified, OXC: oxcarbazepine, PAL: paliperidone, PER: perphenazine, PLA: placebo, QUE: quetiapine, RDC: Research Diagnostic Criteria, RIS-LAI: risperidone long-acting injectable, SAE: serious adverse event, TAU: treatment-as-usual (TAU consisted of any number or combinations of antidepressants, mood stabilizers or anxiolytics), VAL: valproate, YMRS: Young Mania Rating Scale, yr: year, wk: week, ZIP: ziprasidone
Supplementary Table 2. The primary outcome (or main outcome) of the individual study included in our systematic review

**Supplementary Table 2-1. Monotherapy studies**

| Study name          | The primary outcome (or main outcome) of the individual study* |
|---------------------|---------------------------------------------------------------|
| Amsterdam 2010      | Time to relapse or recurrence of depressive episodes (LIT vs PLA): not information |
| Berwaerts 2012      | Time to recurrence of any mood symptoms: PAL > PLA |
| Bowden 2000         | Time to recurrence of any mood episode: DIV = PLA, DIV = LIT, LIT = PLA |
| Bowden 2003         | Time to intervention for any mood episode: LAM > PLA, LIT > PLA, LAM = LIT |
| Calabrese 2000      | Time to additional pharmacotherapy for emerging symptoms: LAM = PLA |
| Calabrese 2003      | Time to additional pharmacotherapy for emerging symptoms: LAM > PLA, LIT > PLA, LAM = LIT |
| Calabrese 2005      | Time to treatment for a mood episode: DIV = LIT |
| Calabrese 2017b     | Time to recurrence of any mood episode: AOM > PLA |
| Coxhead 1992        | Relapse rate: CAR = LIT |
| Cundall 1972        | Relapse rate: LIT > PLA |
| Dunner 1976         | Hypomanic episodes/patient year: LIT > PLA, depressive episodes/patient year: LIT = PLA |
| Fieve 1976          | Frequency of depressive episodes: LIT > PLA, dropouts due to depression: LIT > PLA |
| Geddes 2010         | Initiation of new intervention for an emergent mood episode: LIT+VAL > VAL, LIT+VAL > LIT, LIT > VAL |
| Hartong 2003        | Recurrence of an episode of (hypo)mania or major depression: LIT > CAR |
| Kane 1982           | Relapses of any type: LIT > PLA |
| Keck 2007           | Time to relapse of any mood episode: ARI > PLA |
| Kleindienst 2000    | Hospitalization: LIT > CAR |
| Koyama 2011         | Time to withdrawal from study: LAM > PLA |
| Melia 1970          | Length of remission: LIT > PLA |
| Prien 1973a         | Number of affective episodes: LIT > PLA |
| Prien 1973b         | Number of affective episodes: LIT > PLA |
| Quiroz 2010         | Time to recurrence for any mood episode: RISLAI > PLA |
| Szegedi 2018        | Time to recurrence of any mood event: ASE > PLA |
| Study name | The primary outcome (or main outcome) of the individual study* |
|------------|---------------------------------------------------------------|
| Tohen 2005 | Symptomatic recurrence of any mood episode following remission of mania or depression: LIT = OLA |
| Tohen 2006 | Time to symptomatic relapse into any mood episode: OLA > PLA |
| Vieta 2012 | Time to recurrence of any mood episode: RISLAI = PLA, OLA > PLA |
| Weisler 2011 | Time to recurrence of any mood episode: QUE > PLA |
| Young 2014 | Time to recurrence of a mood event: QUE > PLA |

**Supplementary Table 2-2. Combination therapy studies**

| Study name | The primary outcome (or main outcome) of the individual study* |
|------------|---------------------------------------------------------------|
| Bowden 2010 | Time to intervention for a mood episode: ZIP+LIT/VAL > PLA+LIT/VAL |
| Bowden 2012 | Time to depressive episode: LAM+DIV = PLA+LAM |
| Calabrese 2017a | Time to recurrence of any mood episode: LUR+LIT/VAL = PLA+LIT/VAL |
| Carlson 2012 | Time from randomization to relapse into a manic/mixed episode: ARI+LAM = PLA+LAM |
| Macfadden 2009 | Time to relapse to any mood episode: RISLAI+TAU > PLA+TAU |
| Marcus 2011 | Time from randomization to relapse due to any mood episode: ARI+LIT/VAL > PLA+LIT/VAL |
| Suppes 2009 | Time to recurrence of any mood event: QUE+LIT/DIV > PLA+LIT/DIV |
| Tohen 2004 | Time to syndromic relapse: OLA+LIT/VAL = PLA+LIT/VAL |
| Vieta 2008a | Length of the remission period: LIT+OXC = LIT+PLA |
| Vieta 2008b | Time to recurrence of any mood event: QUE+LIT/DIV > PLA+LIT/DIV |
| Woo 2011 | Time from randomization to relapse of any mood episode: ARI+DIV = PLA+DIV |
| Yatham 2007 | Safety and efficacy outcomes: RIS-LAI+oral OLA, QUE or RIS = oral OLA, QUE or RIS |
| Zarate 2004 | Time to relapse into depression: PLA + CAR, LIT or VAL > PER + CAR, LIT or VAL |

* A > B means that A was superior to B. AOM: aripiprazole once-monthly, ARI: aripiprazole, ASE: asenapine, CAR: carbamazepine, DIV: divalproex, LAM: lamotrigine, LIT: lithium, LUR: lurasidone, OXC: oxcarbazepine, PAL: paliperidone, PER: perphenazine, PLA: placebo, QUE: quetiapine, RIS-LAI: risperidone long-acting injectable, TAU: treatment-as-usual (TAU consisted of any number or combinations of antidepressants, mood stabilizers or anxiolytics), VAL: valproate, ZIP: ziprasidone
Supplementary Appendix 1. Results of first network meta-analysis.

1.1. Recurrence/relapse rate of any mood episode (29 studies, 6890 patients)
League table

Results from the pairwise meta-analysis are presented in the left lower half and results from the network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|   | AOM          | 0.838 (0.438, 1.604) | 0.978 (0.506, 1.888) | 1.776 (0.630, 5.007) | 1.980 (0.882, 4.443) | 0.759 (0.409, 1.406) | 0.679 (0.420, 1.096) | 0.831 (0.524, 1.319) | 1.267 (0.574, 2.794) | 0.987 (0.557, 1.749) | 1.037 (0.635, 1.692) | 0.621 (0.350, 1.104) | 0.986 (0.597, 1.628) | 0.814 (0.486, 1.363) | 0.818 (0.490, 1.366) | 0.519 (0.335, 0.803) |
|---|-------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
|   | ARI         | 1.166 (0.587, 2.319) | 2.118 (0.737, 6.086) | 2.362 (1.028, 5.428) | 0.905 (0.473, 1.730) | 0.810 (0.482, 1.360) | 0.991 (0.600, 1.638) | 1.511 (0.669, 3.415) | 1.178 (0.643, 2.157) | 1.237 (0.729, 2.098) | 0.741 (0.404, 1.361) | 1.176 (0.685, 2.017) | 0.971 (0.559, 1.687) | 0.976 (0.563, 1.691) | 0.619 (0.383, 0.999) |
|   | ARI+LAM     | 1.816 (0.631, 5.226) | 2.025 (0.875, 4.688) | 0.776 (0.405, 1.485) | 0.694 (0.442, 1.090) | 0.850 (0.514, 1.407) | 1.295 (0.573, 2.390) | 1.010 (0.550, 1.853) | 1.060 (0.620, 1.814) | 0.635 (0.343, 1.744) | 1.008 (0.582, 1.461) | 0.832 (0.474, 1.461) | 0.837 (0.481, 1.545) | 0.530 (0.324, 0.868) | 0.292 (0.114, 0.748) |
|   | ARI+VAL     | 1.115 (0.350, 3.558) | 0.427 (0.154, 1.183) | 0.382 (0.147, 0.995) | 0.468 (0.184, 1.190) | 0.713 (0.230, 2.214) | 0.556 (0.212, 1.455) | 0.584 (0.223, 1.525) | 0.350 (0.127, 0.962) | 0.555 (0.211, 1.461) | 0.458 (0.172, 1.134) | 0.461 (0.187, 1.134) | 0.292 (0.114, 0.748) | 0.748 (0.471, 1.214) | 0.517 (0.333, 0.757) |
|   | ASE         | 0.383 (0.171, 0.859) | 0.343 (0.169, 0.696) | 0.420 (0.209, 0.842) | 0.640 (0.248, 1.649) | 0.499 (0.230, 1.081) | 0.523 (0.256, 1.071) | 0.314 (0.144, 0.682) | 0.498 (0.241, 1.026) | 0.411 (0.197, 0.856) | 0.413 (0.199, 0.858) | 0.262 (0.133, 0.517) | 0.517 (0.333, 0.757) | 0.517 (0.333, 0.757) | 0.517 (0.333, 0.757) |
|   | CAR         | 0.895 (0.561, 1.427) | 1.095 (0.728, 1.649) | 1.670 (0.780, 3.576) | 1.301 (0.762, 2.221) | 1.366 (0.850, 2.197) | 0.819 (0.461, 1.454) | 1.299 (0.796, 2.121) | 1.073 (0.643, 1.791) | 1.078 (0.671, 1.734) | 0.684 (0.442, 1.057) | 1.057 (0.628, 1.734) | 0.930 (0.537, 1.725) | 0.930 (0.537, 1.725) | 0.930 (0.537, 1.725) |
|   | 0.694 (0.442, 1.090) | LAM                 | 1.224 (0.978, 1.533) | 1.866 (0.945, 3.685) | 1.454 (0.968, 2.184) | 1.527 (1.141, 2.044) | 0.915 (0.600, 1.396) | 1.452 (1.063, 1.984) | 1.199 (0.856, 1.679) | 1.205 (0.875, 1.659) | 0.764 (0.428, 1.281) | 0.930 (0.537, 1.725) | 0.930 (0.537, 1.725) | 0.930 (0.537, 1.725) | 0.930 (0.537, 1.725) |
|   | 1.095 (0.728, 1.649) | LIT                 | 1.524 (0.802, 2.897) | 1.188 (0.842, 1.676) | 1.247 (0.980, 1.587) | 0.748 (0.500, 1.118) | 1.186 (0.719, 1.553) | 0.979 (0.723, 1.253) | 0.984 (0.723, 1.253) | 0.624 (0.357, 0.725) | 0.725 (0.437, 1.214) | 0.578 (0.333, 0.957) | 0.578 (0.333, 0.957) | 0.578 (0.333, 0.957) | 0.578 (0.333, 0.957) |
|                | LIT+O | LIT+V | OLA | PAL | RISLAI | VAL | PLA |
|----------------|-------|-------|-----|-----|--------|-----|-----|
| LIT+O XC       | 1.524 (0.802, 2.897) | 0.779 (0.376, 1.615) | 0.818 (0.412, 1.625) | 0.491 (0.230, 1.047) | 0.778 (0.388, 1.562) | 0.642 (0.315, 1.310) | 0.646 (0.325, 1.283) | 0.409 (0.212, 0.792) |
| LIT+V AL       | 1.102 (0.761, 1.595) | 1.050 (0.692, 1.592) | 0.630 (0.372, 1.064) | 0.999 (0.647, 1.540) | 0.824 (0.522, 1.303) | 0.829 (0.591, 1.163) | 0.525 (0.363, 0.760) |
| OLA            | 1.295 (0.877, 1.913) | 0.599 (0.388, 0.926) | 0.951 (0.685, 1.320) | 0.785 (0.566, 1.089) | 0.789 (0.566, 1.100) | 0.500 (0.400, 0.625) |
| PAL            | 0.409 (0.187, 1.134) | 1.007 (0.781, 1.299) | 0.776 (0.543, 1.111) | 0.613 (0.382, 0.983) | 1.586 (1.013, 2.482) | 0.826 (0.571, 1.194) | 0.526 (0.411, 0.674) | 0.835 (0.575, 1.212) |
| RISLAI         | 0.519 (0.335, 0.803) | 0.619 (0.383, 0.999) | 0.262 (0.133, 0.517) | 0.795 (0.647, 0.976) | 0.618 (0.525, 0.728) | 0.521 (0.400, 0.680) | 0.835 (0.575, 1.212) | 0.508 (0.393, 0.657) |
| PLA            | 0.613 (0.485, 0.889) | 0.508 (0.396, 0.997) | 0.628 (0.462, 0.813) | 0.628 (0.462, 0.813) | 0.628 (0.462, 0.813) | 0.628 (0.462, 0.813) | 0.628 (0.462, 0.813) | 0.628 (0.462, 0.813) |
Evaluation of heterogeneity and inconsistency

We inferred the magnitude of heterogeneity by comparing the estimated $\tau^2$ to empirical distributions of heterogeneity typically found in meta-analyses. The predictive $\tau^2$ distribution for mental health outcomes according to Rhodes et al. has a median of 0.049 and an IQR of 0.01 – 0.242. Low heterogeneity could be considered when the estimated $\tau^2$ is less than the 25% quantile of the empirical distribution, moderate heterogeneity for $\tau^2$ between 25% and 50% quantile and high heterogeneity for $\tau^2$ larger than the 50% quantile. We evaluated global consistency under the assumption of a full design-by-treatment interaction model in netmeta.

Rhodes KM, Turner RM, Higgins JPT. Empirical evidence about inconsistency among studies in a pairwise meta-analysis. Research synthesis methods 2016; 7: 346–70.

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|-----------------------------------------------|
| 0.021                            | Low                      | Q=7.776, df=10, p=0.651                       |

Inconsistency

|                               | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures | Ratio of risk ratios | P value  |
|-------------------------------|-----------------|---------------------|----------------------|------------------------|---------------------|----------|
| LAM vs LIT                    | 1.224 (0.978, 1.533) | 1.101 (0.809, 1.499) | 1.380 (0.994, 1.915) | 0.798 (0.509, 1.252) | 0.326               |
| LAM vs PLA                    | 0.764 (0.628, 0.930) | 0.795 (0.647, 0.976) | 0.489 (0.246, 0.975) | 1.624 (0.791, 3.334) | 0.186               |
| LIT vs LIT+VAL                | 1.188 (0.842, 1.676) | 1.102 (0.761, 1.595) | 1.933 (0.754, 4.957) | 0.570 (0.207, 1.567) | 0.276               |
| LIT vs OLA                    | 1.247 (0.980, 1.587) | 1.295 (0.877, 1.913) | 1.219 (0.897, 1.655) | 1.062 (0.647, 1.744) | 0.811               |
| LIT vs QUE                    | 1.186 (0.905, 1.553) | 1.159 (0.792, 1.696) | 1.214 (0.828, 1.780) | 0.954 (0.556, 1.637) | 0.865               |
| LIT vs VAL                    | 0.984 (0.773, 1.253) | 1.007 (0.781, 1.299) | 0.793 (0.364, 1.729) | 1.270 (0.560, 2.884) | 0.567               |
| LIT vs PLA                    | 0.624 (0.537, 0.725) | 0.618 (0.525, 0.728) | 0.653 (0.454, 0.939) | 0.947 (0.636, 1.411) | 0.788               |
| LIT+VAL vs VAL                | 0.829 (0.591, 1.163) | 0.776 (0.543, 1.111) | 1.424 (0.508, 3.990) | 0.545 (0.183, 1.624) | 0.276               |
| OLA vs RISLAI                 | 0.785 (0.566, 1.089) | 0.613 (0.382, 0.983) | 0.987 (0.627, 1.553) | 0.621 (0.322, 1.195) | 0.153               |
| OLA vs PLA                    | 0.500 (0.400, 0.625) | 0.521 (0.400, 0.680) | 0.454 (0.302, 0.683) | 1.149 (0.706, 1.871) | 0.576               |
| QUE vs PLA                    | 0.526 (0.411, 0.674) | 0.508 (0.393, 0.657) | 0.801 (0.330, 1.946) | 0.634 (0.252, 1.598) | 0.334               |
| RISLAI vs PLA                 | 0.637 (0.484, 0.839) | 0.613 (0.462, 0.813) | 1.222 (0.383, 3.898) | 0.502 (0.152, 1.656) | 0.258               |
| VAL vs PLA                    | 0.634 (0.485, 0.829) | 0.628 (0.396, 0.997) | 0.637 (0.458, 0.886) | 0.987 (0.560, 1.740) | 0.963               |
|            | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 | Rank 11 | Rank 12 | Rank 13 | Rank 14 | Rank 15 | Rank 16 |
|------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| AOM        | 0.007  | 0.048  | 0.119  | 0.140  | 0.117  | 0.105  | 0.095  | 0.080  | 0.063  | 0.055  | 0.051  | 0.048  | 0.035  | 0.024  | 0.012  | 0.002  |
| ARI        | 0.004  | 0.021  | 0.045  | 0.064  | 0.069  | 0.074  | 0.075  | 0.079  | 0.073  | 0.077  | 0.081  | 0.094  | 0.086  | 0.083  | 0.054  | 0.022  |
| ARI+LAM    | 0.008  | 0.044  | 0.099  | 0.123  | 0.093  | 0.092  | 0.082  | 0.080  | 0.069  | 0.064  | 0.068  | 0.065  | 0.051  | 0.034  | 0.020  | 0.009  |
| ARI+VAL    | 0.302  | 0.283  | 0.148  | 0.064  | 0.041  | 0.032  | 0.025  | 0.020  | 0.016  | 0.013  | 0.013  | 0.012  | 0.009  | 0.010  | 0.008  | 0.005  |
| ASE        | 0.553  | 0.293  | 0.089  | 0.029  | 0.015  | 0.006  | 0.006  | 0.003  | 0.002  | 0.002  | 0.001  | 0.001  | 0.000  | 0.000  | 0.000  | 0.000  |
| CAR        | 0.000  | 0.001  | 0.003  | 0.008  | 0.013  | 0.019  | 0.024  | 0.037  | 0.041  | 0.058  | 0.083  | 0.116  | 0.153  | 0.197  | 0.171  | 0.079  |
| LAM        | 0.000  | 0.000  | 0.000  | 0.000  | 0.001  | 0.001  | 0.003  | 0.007  | 0.014  | 0.032  | 0.068  | 0.144  | 0.284  | 0.302  | 0.140  | 0.004  |
| LIT        | 0.000  | 0.000  | 0.000  | 0.002  | 0.004  | 0.020  | 0.063  | 0.137  | 0.229  | 0.245  | 0.186  | 0.093  | 0.020  | 0.003  | 0.000  | 0.000  |
| LIT+OXC    | 0.116  | 0.246  | 0.241  | 0.102  | 0.070  | 0.051  | 0.044  | 0.027  | 0.023  | 0.018  | 0.018  | 0.013  | 0.013  | 0.010  | 0.005  | 0.003  |
| LIT+VAL    | 0.005  | 0.027  | 0.097  | 0.152  | 0.139  | 0.127  | 0.124  | 0.097  | 0.075  | 0.054  | 0.040  | 0.029  | 0.018  | 0.011  | 0.004  | 0.001  |
| OLA        | 0.003  | 0.021  | 0.091  | 0.169  | 0.215  | 0.190  | 0.134  | 0.086  | 0.048  | 0.023  | 0.012  | 0.005  | 0.003  | 0.001  | 0.000  | 0.000  |
| PAL        | 0.000  | 0.001  | 0.001  | 0.003  | 0.006  | 0.006  | 0.012  | 0.017  | 0.019  | 0.029  | 0.046  | 0.075  | 0.127  | 0.194  | 0.304  | 0.160  |
| QUE        | 0.002  | 0.013  | 0.057  | 0.122  | 0.157  | 0.173  | 0.157  | 0.118  | 0.082  | 0.052  | 0.035  | 0.021  | 0.010  | 0.004  | 0.001  | 0.000  |
| RISLAI     | 0.000  | 0.001  | 0.007  | 0.014  | 0.032  | 0.055  | 0.079  | 0.098  | 0.109  | 0.121  | 0.148  | 0.153  | 0.102  | 0.058  | 0.021  | 0.002  |
| VAL        | 0.000  | 0.001  | 0.003  | 0.010  | 0.031  | 0.051  | 0.078  | 0.115  | 0.138  | 0.158  | 0.150  | 0.131  | 0.086  | 0.036  | 0.013  | 0.000  |
| PLA        | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.003  | 0.036  | 0.249  | 0.712  |
| Comparison | SUCRA |
|------------|-------|
| ARI+VAL    | 0.85  |
| LIT+OXC    | 0.83  |
| ASE        | 0.81  |
| OLA        | 0.78  |
| LIT+VAL    | 0.70  |
| ARI+LAM    | 0.55  |
| AOM        | 0.53  |
| QUE        | 0.52  |
| LIT        | 0.49  |
| RISLAI     | 0.42  |
| VAL        | 0.41  |
| ARI        | 0.40  |
| CAR        | 0.30  |
| LAM        | 0.23  |
| PAL        | 0.16  |
| PLA        | 0.02  |
CINeMA confidence rating

(1) Within-study bias
We referred to the following article:
Furukawa TA, et al., Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis. BMJ Open. 2016 Jul 8;6(7):e010919. doi: 10.1136/bmjopen-2015-010919.

(2) Reporting bias
Comparison-adjusted funnel plots with fewer than ten studies are not meaningful. Therefore, all comparisons were “Major concerns.”

(3) Indirectness
No indirectness assumed.

(3) Imprecision
A clinically meaningful threshold was set at a risk ratio of higher or lower than 1.

(4) Heterogeneity
We used recommendations automatically provided by CINeMA.

(5) Incoherence
We used recommendations automatically provided by CINeMA.
| Comparison         | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|--------------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|-------------------|
| AOM:PLA            | 1                 | No concerns       | Suspected      | No concerns  | No concerns  | No concerns   | No concerns  | Moderate          |
| ARI:PLA            | 1                 | No concerns       | Suspected      | No concerns  | No concerns  | Major concerns| No concerns  | Low               |
| ARI+LAM:LAM        | 1                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| ARI+VAL:VAL        | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Very low          |
| ASE:PLA            | 1                 | No concerns       | Suspected      | No concerns  | No concerns  | No concerns   | No concerns  | Moderate          |
| CAR:LIT            | 3                 | Major concerns    | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Very low          |
| LAM:LIT            | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Very low          |
| LAM:PLA            | 4                 | Some concerns     | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Very low          |
| LIT:LIT+OXC        | 1                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| LIT:LIT+VAL        | 1                 | Major concerns    | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Very low          |
| LIT:OLA            | 1                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| LIT:PLA            | 10                | Some concerns     | Suspected      | No concerns  | No concerns  | No concerns   | No concerns  | Low               |
| LIT:QUE            | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Very low          |
| LIT:VAL            | 3                 | Major concerns    | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Very low          |
| LIT+VAL:VAL        | 1                 | Major concerns    | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Very low          |
| OLA:PLA            | 2                 | No concerns       | Suspected      | No concerns  | No concerns  | No concerns   | No concerns  | Moderate          |
| OLA:RISLAI         | 1                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| PAL:PLA            | 1                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| PLA:QUE            | 2                 | Some concerns     | Suspected      | No concerns  | No concerns  | No concerns   | No concerns  | Low               |
| PLA:RISLAI         | 2                 | No concerns       | Suspected      | No concerns  | No concerns  | No concerns   | No concerns  | Moderate          |
| PLA:VAL            | 1                 | No concerns       | Suspected      | No concerns  | No concerns  | No concerns   | No concerns  | Moderate          |
| AOM:ARI            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| AOM:ARI+LAM        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| AOM:ARI+VAL        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| AOM:ASE            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| AOM:CAR            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| AOM:LAM            | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Very low          |
| AOM:LIT            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| AOM:LIT+OXC        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| AOM:LIT+VAL        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| AOM:OLA            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| AOM:PAL            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns| No concerns   | No concerns  | Low               |
| Combination                | Concerns | Suspected | Major Concerns | No Concerns | No Concerns | No Concerns | Low |
|---------------------------|----------|-----------|----------------|-------------|-------------|-------------|-----|
| AOM:QUE                   | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| AOM:RISLAI                | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| AOM:VAL                   | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI:ARI+LAM               | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI:ARI+VAL               | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI:ASE                   | 0        | No concerns | No concerns | No concerns | Major concerns | No concerns | Low |
| ARI:CAR                   | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARILAM                    | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARILIT                    | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARILIT+OXC                | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARILIT+VAL                | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARIQUE                    | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+LAM:ARI+VAL           | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+LAM:ASE               | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+LAM:CAR               | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+LAM:LAM               | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+LAM:LIT+OXC           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+LAM:LIT+VAL           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+LAM:OLA               | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+LAM:PAL               | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+LAM:QUE               | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+LAM+RISLAI            | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+LAM:VAL               | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+VAL:ASE               | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| ARI+VAL:CAR               | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+VAL:LAM               | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+VAL:LIT               | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+VAL:LIT+OXC           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| Combination         | Major concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
|---------------------|----------------|-----------|-------------|----------------|-------------|-------------|----------|
| ARI+VAL:LIT+VAL     | 0              | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+VAL:OLA         | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| ARI+VAL:PAL         | 0              | No concerns | Suspected | No concerns | No concerns | Major concerns | Low |
| ARI+VAL:PLA         | 0              | Some concerns | Suspected | No concerns | No concerns | No concerns | Low     |
| ARI+VAL:QUE         | 0              | Some concerns | Suspected | No concerns | Major concerns | No concerns | Very low |
| ARI+VAL:RISLAI      | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| ASE:CAR             | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Moderate |
| ASE:PLE             | 0              | Some concerns | Suspected | No concerns | No concerns | No concerns | Low     |
| ASE:QUE             | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| ASE:RISLAI          | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| CAR:OLA             | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| CAR:PAL             | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| CAR:PLA             | 0              | Some concerns | Suspected | No concerns | Major concerns | No concerns | Very low |
| CAR:QUE             | 0              | Some concerns | Suspected | No concerns | Major concerns | No concerns | Very low |
| CAR:RISLAI          | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| LAM:LIT+OXC         | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Very low |
| LAM:LIT+VAL         | 0              | Major concerns | Suspected | No concerns | Major concerns | No concerns | Very low |
| LAM:OLA             | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| LAM:PAL             | 0              | Some concerns | Suspected | No concerns | Major concerns | No concerns | Very low |
| LAM:QUE             | 0              | Some concerns | Suspected | No concerns | Major concerns | No concerns | Very low |
| LAM:RISLAI          | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| LIT:PAL             | 0              | No concerns | Suspected | No concerns | Major concerns | No concerns | Low     |
| Combinations | Concerns | Suspected | Major Concerns | No Concerns | No Concerns | No Concerns | Low |
|--------------|----------|-----------|----------------|-------------|-------------|-------------|-----|
| LIT:RISLAI   | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT+OXC:LIT+VAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT+OXC:OLA | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT+OXC:PAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT+OXC:PLA | 0 | No concerns | Suspected | No concerns | No concerns | No concerns | Moderate |
| LIT+OXC:QUE | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT+OXC:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT+OXC:VAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT+VAL:OLA | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT+VAL:PAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT+VAL:PLA | 0 | Major concerns | Suspected | No concerns | No concerns | No concerns | Low |
| LIT+VAL:QUE | 0 | Major concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
| LIT+VAL:RISLAI | 0 | No concerns | Suspected | No concerns | No concerns | No concerns | Low |
| OLA:PAL     | 0 | No concerns | Suspected | No concerns | No concerns | Major concerns | No concerns | Low |
| OLA:QUE     | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| OLA:VAL     | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| PAL:QUE     | 0 | No concerns | Suspected | No concerns | No concerns | Major concerns | No concerns | Low |
| PAL:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| PAL:VAL     | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| QUE:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| QUE:VAL     | 0 | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
| RISLAI:VAL  | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| Meta-regression analysis | Primary analysis | Publication year | Duration of study | Number of total patients | Percent female | Mean age |
|--------------------------|------------------|------------------|------------------|--------------------------|--------------|---------|
| Heterogeneity SD         | 0.145            | 0.164            | 0.262            | 0.153                    | 0.118        | 0.164   |
| Relative change in the variance $\beta$, median (95% CI) | +13% (0.076 (-0.220, 0.412)) | +81% (-0.460 (-1.084, 0.306)) | +6% (-0.066 (-0.244, 0.157)) | -19% (0.253 (-0.065, 0.533)) | +13% (-0.008 (-0.357, 0.300)) |
| Interventions vs placebo |                  |                  |                  |                          |              |         |
| AOM RR (95% CI)          | 0.519 (0.335, 0.803) | 0.492 (0.285, 0.812) | 0.302 (0.136, 0.697) | 0.514 (0.313, 0.822)    | 0.509 (0.328, 0.776) | 0.510 (0.308, 0.844) |
| ARI RR (95% CI)          | 0.619 (0.383, 0.999) | 0.601 (0.350, 1.017) | 0.521 (0.198, 1.304) | 0.603 (0.355, 1.008)    | 0.546 (0.331, 0.900) | 0.608 (0.346, 1.029) |
| ARI+LAM RR (95% CI)      | 0.530 (0.324, 0.868) | 0.535 (0.304, 0.919) | 0.303 (0.119, 0.747) | 0.535 (0.311, 0.898)    | 0.545 (0.336, 0.879) | 0.533 (0.304, 0.923) |
| ARI+VAL RR (95% CI)      | 0.292 (0.114, 0.748) | 0.317 (0.120, 0.791) | 0.145 (0.034, 0.519) | 0.318 (0.115, 0.792)    | 0.334 (0.129, 0.786) | 0.320 (0.120, 0.788) |
| ASE RR (95% CI)          | 0.262 (0.133, 0.517) | 0.243 (0.109, 0.476) | 0.138 (0.048, 0.387) | 0.253 (0.119, 0.498)    | 0.258 (0.125, 0.489) | 0.251 (0.118, 0.504) |
| CAR RR (95% CI)          | 0.684 (0.442, 1.057) | 0.761 (0.490, 1.211) | 0.502 (0.247, 1.066) | 0.765 (0.499, 1.189)    | 0.787 (0.531, 1.188) | 0.748 (0.484, 1.203) |
| LAM RR (95% CI)          | 0.764 (0.628, 0.930) | 0.754 (0.599, 0.939) | 0.507 (0.325, 0.777) | 0.763 (0.609, 0.940)    | 0.777 (0.635, 0.935) | 0.756 (0.600, 0.941) |
| LIT RR (95% CI)          | 0.624 (0.537, 0.725) | 0.620 (0.517, 0.743) | 0.379 (0.270, 0.504) | 0.626 (0.522, 0.734)    | 0.649 (0.549, 0.750) | 0.611 (0.514, 0.722) |
| LIT+OXC RR (95% CI)      | 0.409 (0.212, 0.792) | 0.387 (0.184, 0.777) | 0.161 (0.042, 0.593) | 0.396 (0.188, 0.770)    | 0.401 (0.197, 0.778) | 0.388 (0.184, 0.766) |
| LIT+VAL RR (95% CI)      | 0.525 (0.363, 0.760) | 0.521 (0.334, 0.799) | 0.253 (0.108, 0.556) | 0.525 (0.342, 0.775)    | 0.546 (0.371, 0.773) | 0.514 (0.331, 0.779) |
| OLA RR (95% CI)          | 0.500 (0.400, 0.625) | 0.489 (0.371, 0.621) | 0.227 (0.141, 0.355) | 0.506 (0.379, 0.636)    | 0.505 (0.398, 0.617) | 0.493 (0.365, 0.635) |
| PAL RR (95% CI)          | 0.835 (0.575, 1.212) | 0.801 (0.502, 1.264) | 1.306 (0.365, 4.010) | 0.833 (0.545, 1.259)    | 0.858 (0.586, 1.242) | 0.829 (0.524, 1.289) |
| QUE RR (95% CI)          | 0.526 (0.411, 0.674) | 0.508 (0.377, 0.690) | 0.362 (0.222, 0.574) | 0.557 (0.388, 0.774)    | 0.526 (0.413, 0.671) | 0.519 (0.382, 0.699) |
| RISLAI RR (95% CI)       | 0.637 (0.484, 0.839) | 0.614 (0.447, 0.858) | 0.461 (0.255, 0.801) | 0.638 (0.472, 0.874)    | 0.672 (0.504, 0.883) | 0.627 (0.444, 0.884) |
| VAL RR (95% CI)          | 0.634 (0.485, 0.829) | 0.625 (0.455, 0.844) | 0.414 (0.228, 0.681) | 0.633 (0.461, 0.839)    | 0.665 (0.491, 0.858) | 0.618 (0.450, 0.832) |
| Sensitivity analysis | Model fit statistics | Primary analysis | Focusing on studies including only BDI | Focusing on studies including only non rapid-cycling BD patients | Focusing on double-blind studies | Focusing on non-enriched studies | Focusing on non-industry sponsorship studies |
|---------------------|----------------------|------------------|--------------------------------------|---------------------------------------------------------------|---------------------------------|-----------------------------------|-----------------------------------------------|
| Heterogeneity SD    | 0.145                | 0.142            | 0.103                                | 0.147                                                         | 0.115                          | 0.103                             |
| Relative change in the variance | -2%                 | -29%             | +1%                                  | -21%                                                          | -29%                           |                                   |
| Interventions vs placebo | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) |
| AOM                 | 0.519 (0.335, 0.803) | 0.514 (0.324, 0.816) | 0.506 (0.334, 0.770) | 0.514 (0.319, 0.808) | 0.507 (0.281, 0.880) | 0.506 (0.289, 0.848) |
| ARI                 | 0.619 (0.383, 0.999) | 0.607 (0.364, 0.994) | 0.598 (0.310, 1.062) | 0.609 (0.356, 1.011) | 0.601 (0.309, 1.082) | 0.597 (0.305, 1.107) |
| ARI+LAM             | 0.530 (0.324, 0.868) | 0.531 (0.315, 0.882) | 0.543 (0.293, 0.982) | 0.539 (0.317, 0.931) | 0.548 (0.293, 0.996) | 0.545 (0.294, 0.988) |
| ARI+VAL             | 0.292 (0.114, 0.748) | 0.320 (0.117, 0.780) | 0.363 (0.099, 1.136) | 0.316 (0.113, 0.781) | 0.366 (0.092, 1.077) | 0.351 (0.086, 1.125) |
| ASE                 | 0.262 (0.133, 0.517) | 0.251 (0.115, 0.480) | 0.251 (0.121, 0.473) | 0.250 (0.117, 0.493) | 0.246 (0.088, 0.577) | 0.246 (0.090, 0.576) |
| CAR                 | 0.684 (0.442, 1.057) | 0.766 (0.448, 1.349) | 0.759 (0.440, 1.307) | 0.798 (0.501, 1.306) | 0.749 (0.505, 1.132) | 0.670 (0.444, 1.028) |
| LAM                 | 0.764 (0.628, 0.930) | 0.753 (0.601, 0.927) | 0.764 (0.602, 0.950) | 0.762 (0.614, 0.930) | 0.767 (0.599, 0.954) | 0.767 (0.600, 0.953) |
| LIT                 | 0.624 (0.537, 0.725) | 0.618 (0.522, 0.724) | 0.604 (0.504, 0.723) | 0.613 (0.521, 0.717) | 0.618 (0.520, 0.728) | 0.599 (0.506, 0.701) |
| LIT+OXC             | 0.409 (0.212, 0.792) | 0.378 (0.136, 0.889) | 0.363 (0.130, 0.833) | 0.389 (0.187, 0.749) | 0.385 (0.190, 0.729) | 0.379 (0.193, 0.719) |
| LIT+VAL             | 0.525 (0.363, 0.760) | 0.520 (0.348, 0.781) | 0.511 (0.331, 0.774) | 0.507 (0.317, 0.780) | 0.525 (0.357, 0.749) | 0.512 (0.353, 0.729) |
| OLA                 | 0.500 (0.400, 0.625) | 0.498 (0.386, 0.625) | 0.493 (0.383, 0.614) | 0.498 (0.381, 0.624) | 0.504 (0.389, 0.634) | 0.503 (0.389, 0.640) |
| PAL                 | 0.835 (0.575, 1.212) | 0.825 (0.555, 1.219) | 0.827 (0.579, 1.186) | 0.828 (0.551, 1.249) | 0.827 (0.530, 1.268) | 0.817 (0.532, 1.254) |
| QUE                 | 0.526 (0.411, 0.674) | 0.508 (0.384, 0.688) | 0.508 (0.386, 0.678) | 0.520 (0.396, 0.682) | 0.514 (0.384, 0.689) | 0.510 (0.384, 0.675) |
| RISLAI              | 0.637 (0.484, 0.839) | 0.633 (0.468, 0.839) | 0.624 (0.481, 0.804) | 0.632 (0.469, 0.850) | 0.629 (0.446, 0.873) | 0.623 (0.450, 0.854) |
| VAL                 | 0.634 (0.485, 0.829) | 0.634 (0.460, 0.830) | 0.625 (0.456, 0.852) | 0.611 (0.448, 0.814) | 0.635 (0.472, 0.825) | 0.629 (0.469, 0.817) |
1.2. Recurrence/relapse of depressive episodes (25 RCTs, 6438 patients)
|        | AOM            | ARI            | ARI+LAM        | ARI+VAL        | ASE            | CAR            |
|--------|----------------|----------------|----------------|----------------|----------------|----------------|
|        | 1.178 (0.440, 3.153) | 1.569 (0.591, 4.164) | 2.098 (0.513, 8.587) | 0.711 (0.138, 3.666) | 0.141 (0.024, 0.837) | 3.826 (0.876, 16.715) |
| AOM    | 2.758 (0.837, 9.091) | 2.341 (0.652, 8.412) | 1.492 (0.456, 4.882) | 0.383 (0.104, 1.409) | 0.539 (0.188, 1.550) | 5.810 (1.243, 27.161) |
|        | 3.879 (0.935, 16.087) | 2.126 (0.650, 2.847) | 0.804 (0.044, 1.010) | 0.582 (0.014, 2.310) | 0.539 (0.017, 1.550) | 3.450 (0.812, 14.667) |
|        | (1.006, 5.065) | 1.917 (0.575, 4.860) | 1.221 (0.604, 2.468) | 0.346 (0.097, 2.135) | 0.486 (0.172, 1.373) | (1.243, 27.161) |
| AOM    | 2.258 (1.006, 5.065) | 1.138 (0.517, 2.508) | 0.725 (0.395, 1.333) | 0.930 (0.160, 5.392) | 1.308 (0.265, 6.450) | 9.279 (1.405, 61.283) |
|        | 1.341 (0.706, 2.546) | 3.061 (0.720, 13.008) | 1.951 (0.503, 7.572) | 0.369 (0.102, 1.338) | 0.519 (0.171, 1.495) | 3.683 (0.821, 16.524) |
|        | 3.606 (0.915, 14.208) | 1.215 (0.536, 2.935) | 0.774 (0.375, 1.493) | 0.369 (0.100, 1.363) | 0.518 (0.180, 1.495) | 3.679 (0.838, 16.518) |
|        | 1.431 (0.675, 3.034) | 1.214 (0.536, 2.749) | 0.773 (0.375, 1.493) | 0.209 (0.053, 0.826) | 0.293 (0.094, 0.915) | 2.082 (0.446, 9.725) |
|        | 1.430 (0.728, 2.808) | 0.809 (0.367, 1.786) | 0.438 (0.201, 0.955) | 0.209 (0.053, 0.826) | 0.293 (0.094, 0.915) | 5.692 (1.295, 25.011) |
|        | 0.809 (0.367, 1.786) | 2.212 (1.127, 4.342) | 0.438 (0.201, 0.955) | 0.209 (0.053, 0.826) | 0.293 (0.094, 0.915) | 0.554 (0.342, 0.899) |
|        | 0.824 (0.394, 1.722) | 1.251 (0.616, 2.541) | 0.438 (0.201, 0.955) | 0.209 (0.053, 0.826) | 0.293 (0.094, 0.915) | 0.554 (0.342, 0.899) |
|        | 0.824 (0.394, 1.722) | 1.251 (0.616, 2.541) | 0.438 (0.201, 0.955) | 0.209 (0.053, 0.826) | 0.293 (0.094, 0.915) | 0.554 (0.342, 0.899) |
|        | 1.141 (0.351, 3.146) | 1.308 (0.456, 4.882) | 0.725 (0.395, 1.333) | 0.930 (0.160, 5.392) | 1.308 (0.265, 6.450) | 9.279 (1.405, 61.283) |
|        | 1.141 (0.351, 3.146) | 1.308 (0.456, 4.882) | 0.725 (0.395, 1.333) | 0.930 (0.160, 5.392) | 1.308 (0.265, 6.450) | 9.279 (1.405, 61.283) |
|        | 1.141 (0.351, 3.146) | 1.308 (0.456, 4.882) | 0.725 (0.395, 1.333) | 0.930 (0.160, 5.392) | 1.308 (0.265, 6.450) | 9.279 (1.405, 61.283) |
| AOM    | 0.804 (0.469, 1.379) | 1.518 (0.966, 2.386) | 0.594 (0.349, 1.012) | 1.597 (0.425, 6.003) | 0.634 (0.327, 1.230) | 0.358 (0.174, 0.739) |
|        | 0.804 (0.469, 1.379) | 1.518 (0.966, 2.386) | 0.594 (0.349, 1.012) | 1.597 (0.425, 6.003) | 0.634 (0.327, 1.230) | 0.358 (0.174, 0.739) |
| AOM    | 0.804 (0.469, 1.379) | 1.518 (0.966, 2.386) | 0.594 (0.349, 1.012) | 1.597 (0.425, 6.003) | 0.634 (0.327, 1.230) | 0.358 (0.174, 0.739) |
|        | 0.804 (0.469, 1.379) | 1.518 (0.966, 2.386) | 0.594 (0.349, 1.012) | 1.597 (0.425, 6.003) | 0.634 (0.327, 1.230) | 0.358 (0.174, 0.739) |
|        | 0.804 (0.469, 1.379) | 1.518 (0.966, 2.386) | 0.594 (0.349, 1.012) | 1.597 (0.425, 6.003) | 0.634 (0.327, 1.230) | 0.358 (0.174, 0.739) |

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.
|          | LIT    | LIT+O  | LIT+V  | OLA    | PAL    | QUE    | RISLAI | VAL   | PLA  |
|----------|--------|--------|--------|--------|--------|--------|--------|-------|------|
| 3.450    | 2.690  | 0.224  | 0.399  | 0.566  | 2.734  | 0.373  | 1.518  | 0.900 | 0.791|
| (0.812, | (0.800,| (0.060,| (0.606,| (0.320,| (1.546,| (0.228,| (1.518,| (0.417,| (0.660,|
| 14.667) | 9.039) | 0.842) | 1.647) | 1.001) | 4.834) | 0.609) | 2.593) | 1.942) | 0.948)|
| 0.832    | 1.067  | 0.613  | 0.999  | 1.547  | 0.576  | 0.566  | 1.518  | 0.900 |      |
| (0.591, | (0.716,| (0.114,| (0.606,| (1.049,| (0.365,| (0.366,| (1.518,| (0.417,|      |
| 1.171)   | 1.590) | 1.385) | 1.093) | 2.282) | 0.910) | 0.874) | 2.593) | 1.942) |      |
| 1.066    | 1.650  | 0.613  | 0.565  | 1.546  | 0.576  | 0.566  | 1.518  | 0.900 |      |
| (0.783, | (1.208,| (0.936,| (0.936,| (1.546,| (0.365,| (0.366,| (1.518,| (0.417,|      |
| 1.452)   | 2.252) | 1.039) | 2.552) | 4.834) | 0.910) | 0.874) | 2.593) | 1.942) |      |
| 0.604    | 0.615  | 0.613  | 0.565  | 1.546  | 0.576  | 0.566  | 1.518  | 0.900 |      |
| (0.355, | (0.395,| (0.936,| (0.936,| (1.546,| (0.365,| (0.366,| (1.518,| (0.417,|      |
| 1.026)   | (0.956)| 1.039) | 2.552) | 4.834) | 0.910) | 0.874) | 2.593) | 1.942) |      |
| 1.061    | 0.615  | 0.613  | 0.565  | 1.546  | 0.576  | 0.566  | 1.518  | 0.900 |      |
| (0.573, | (0.395,| (0.936,| (1.546,| (0.365,| (0.366,| (1.518,| (1.518,| (0.417,|      |
| 1.962)   | (0.956)| 1.039) | 2.552) | 4.834) | 0.910) | 0.874) | 2.593) | 1.942) |      |
| 0.748    | 0.402  | 0.322  | 0.780  | 0.373  | 0.566  | 0.480  |          |      |      |
| (0.563, | (0.191,| (0.094,| (0.531,| (0.228,| (0.366,| (0.364,|          |      |      |
| 0.992)   | (0.848)| 1.107) | 1.145) | 0.609) | 0.874) | 0.633) |          |      |      |
Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|----------------------------------------------------|
|                                  |                          | Q        | df | p          |
| 0.011                            | Low                      | 12.796  | 10 | 0.235      |

Inconsistency

|                  | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures |
|------------------|-----------------|--------------------|----------------------|------------------------|
|                  |                 |                    |                      | Ratio of risk ratios    | P value               |
| LAM vs LIT       | 0.902 (0.680, 1.196) | 0.832 (0.591, 1.171) | 1.069 (0.650, 1.759) | 0.778 (0.425, 1.423)   | 0.415                 |
| LAM vs PLA       | 0.713 (0.547, 0.930) | 0.748 (0.563, 0.992) | 0.511 (0.240, 1.088) | 1.463 (0.653, 3.281)   | 0.355                 |
| LIT vs LIT+VAL   | **1.067 (0.716, 1.590)** | **0.897 (0.587, 1.372)** | **3.875 (1.217, 12.333)** | **0.232 (0.067, 0.795)** | **0.020**             |
| LIT vs OLA       | 1.066 (0.783, 1.452) | 0.972 (0.546, 1.731) | 1.107 (0.768, 1.594) | 0.878 (0.443, 1.739)   | 0.709                 |
| LIT vs QUE       | 1.650 (1.208, 2.252) | 1.511 (0.958, 2.381) | 1.783 (1.163, 2.733) | 0.847 (0.454, 1.582)   | 0.603                 |
| LIT vs VAL       | 0.933 (0.680, 1.280) | 0.865 (0.623, 1.200) | 2.585 (0.777, 8.601) | 0.335 (0.096, 1.163)   | 0.085                 |
| LIT vs PLA       | 0.791 (0.660, 0.948) | 0.828 (0.681, 1.006) | 0.593 (0.362, 0.970) | 1.397 (0.822, 2.373)   | 0.216                 |
| LIT+VAL vs VAL   | **0.874 (0.603, 1.268)** | **0.780 (0.531, 1.145)** | **4.823 (1.090, 21.336)** | **0.162 (0.035, 0.751)** | **0.020**             |
| OLA vs RISLAI    | 0.576 (0.365, 0.910) | 0.484 (0.246, 0.951) | 0.668 (0.359, 1.241) | 0.724 (0.289, 1.813)   | 0.491                 |
| OLA vs VAL       | 0.742 (0.562, 0.979) | 0.718 (0.524, 0.984) | 0.832 (0.461, 1.501) | 0.863 (0.442, 1.684)   | 0.666                 |
| QUE vs PLA       | 0.480 (0.364, 0.633) | 0.463 (0.349, 0.615) | 0.978 (0.273, 3.497) | 0.474 (0.128, 1.748)   | 0.262                 |
| RISLAI vs PLA    | 1.287 (0.857, 1.932) | 1.212 (0.791, 1.857) | 2.304 (0.611, 8.686) | 0.526 (0.130, 2.120)   | 0.366                 |
| VAL vs PLA       | **0.848 (0.596, 1.206)** | **0.402 (0.191, 0.848)** | **1.050 (0.704, 1.566)** | **0.383 (0.164, 0.893)** | **0.026**             |
## Rank probabilities

|       | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 | Rank 11 | Rank 12 | Rank 13 | Rank 14 | Rank 15 | Rank 16 | Rank 17 |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| AOM   | 0.000  | 0.002  | 0.005  | 0.009  | 0.019  | 0.023  | 0.033  | 0.038  | 0.043  | 0.049  | 0.062  | 0.097  | 0.124  | 0.157  | 0.161  | 0.151  | 0.028  |
| ARI   | 0.007  | 0.014  | 0.027  | 0.039  | 0.056  | 0.064  | 0.069  | 0.057  | 0.057  | 0.059  | 0.069  | 0.092  | 0.089  | 0.103  | 0.093  | 0.087  | 0.019  |
| ARI+LAM | 0.013  | 0.041  | 0.090  | 0.121  | 0.148  | 0.153  | 0.100  | 0.075  | 0.052  | 0.046  | 0.048  | 0.043  | 0.028  | 0.023  | 0.013  | 0.006  | 0.001  |
| ARI+VAL | 0.293  | 0.259  | 0.154  | 0.086  | 0.053  | 0.040  | 0.023  | 0.016  | 0.016  | 0.011  | 0.014  | 0.008  | 0.007  | 0.006  | 0.004  | 0.002  |
| ASE   | 0.211  | 0.252  | 0.192  | 0.096  | 0.066  | 0.046  | 0.032  | 0.021  | 0.014  | 0.016  | 0.016  | 0.014  | 0.009  | 0.007  | 0.005  | 0.004  | 0.000  |
| CAR   | 0.000  | 0.000  | 0.001  | 0.001  | 0.002  | 0.002  | 0.003  | 0.003  | 0.003  | 0.004  | 0.004  | 0.008  | 0.010  | 0.018  | 0.036  | 0.070  | 0.838  |
| LAM   | 0.000  | 0.000  | 0.002  | 0.010  | 0.043  | 0.117  | 0.200  | 0.192  | 0.164  | 0.131  | 0.079  | 0.043  | 0.016  | 0.004  | 0.001  | 0.000  | 0.000  |
| LAM+VAL | 0.042  | 0.125  | 0.211  | 0.235  | 0.161  | 0.094  | 0.050  | 0.027  | 0.019  | 0.011  | 0.010  | 0.008  | 0.004  | 0.003  | 0.001  | 0.001  | 0.000  |
| LIT   | 0.000  | 0.000  | 0.000  | 0.001  | 0.005  | 0.017  | 0.048  | 0.116  | 0.201  | 0.247  | 0.213  | 0.118  | 0.029  | 0.005  | 0.001  | 0.000  | 0.000  |
| LIT+OXC | 0.426  | 0.246  | 0.127  | 0.062  | 0.046  | 0.030  | 0.016  | 0.012  | 0.009  | 0.007  | 0.006  | 0.005  | 0.003  | 0.003  | 0.002  | 0.001  | 0.000  |
| LIT+VAL | 0.001  | 0.006  | 0.017  | 0.044  | 0.074  | 0.115  | 0.128  | 0.126  | 0.114  | 0.107  | 0.103  | 0.074  | 0.041  | 0.029  | 0.017  | 0.006  | 0.001  |
| OLA   | 0.000  | 0.002  | 0.004  | 0.015  | 0.048  | 0.100  | 0.143  | 0.165  | 0.148  | 0.130  | 0.122  | 0.082  | 0.032  | 0.009  | 0.003  | 0.000  | 0.000  |
| PAL   | 0.000  | 0.000  | 0.000  | 0.000  | 0.003  | 0.004  | 0.008  | 0.009  | 0.012  | 0.018  | 0.025  | 0.042  | 0.078  | 0.137  | 0.238  | 0.359  | 0.067  |
| QUE   | 0.008  | 0.054  | 0.167  | 0.273  | 0.249  | 0.140  | 0.056  | 0.029  | 0.014  | 0.005  | 0.003  | 0.002  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  |
| RISLAI | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.004  | 0.007  | 0.011  | 0.023  | 0.044  | 0.091  | 0.166  | 0.311  | 0.293  | 0.044  |
| VAL   | 0.000  | 0.001  | 0.003  | 0.008  | 0.028  | 0.057  | 0.087  | 0.111  | 0.129  | 0.140  | 0.161  | 0.135  | 0.077  | 0.039  | 0.020  | 0.006  | 0.000  |
| PLA   | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.002  | 0.009  | 0.042  | 0.185  | 0.365  | 0.294  | 0.091  | 0.013  | 0.000  |
### SUCRA

| Comparison            | SUCRA |
|-----------------------|-------|
| ARI+VAL              | 0.89  |
| LIT+OXC              | 0.88  |
| LAM+VAL              | 0.88  |
| QUE                  | 0.75  |
| ASE                  | 0.74  |
| ARI+LAM              | 0.68  |
| LAM                  | 0.57  |
| LIT+VAL              | 0.54  |
| OLA                  | 0.50  |
| LIT                  | 0.47  |
| VAL                  | 0.44  |
| ARI                  | 0.34  |
| AOM                  | 0.25  |
| PLA                  | 0.24  |
| RISLAI               | 0.14  |
| PAL                  | 0.14  |
| CAR                  | 0.05  |
| Comparison       | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|-------------------|
| AOM:PLA          | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI:PLA          | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+LAM:LAM      | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+VAL:VAL      | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| ASE:PLA          | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| CAR:LIT          | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LAM:LAM+VAL      | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LAM:LIT          | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LAM:PLA          | 3                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:LAM+OXC      | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:LIT+OXC      | 1                 | Major concerns    | Suspected      | No concerns  | Major concerns | No concerns | Major concerns | Very low          |
| LIT:OLA          | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:OLA+RISLAI   | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:PLA          | 8                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:QUE          | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:QUE          | 1                 | Some concerns     | Suspected      | No concerns  | No concerns    | No concerns | No concerns | Low               |
| LIT:LAM+OXC      | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:LIT+OXC      | 1                 | Major concerns    | Suspected      | No concerns  | Major concerns | No concerns | Major concerns | Very low          |
| LIT:OLA+RISLAI   | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PAL:PLA          | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PLA:QUE          | 2                 | Some concerns     | Suspected      | No concerns  | No concerns    | No concerns | No concerns | Low               |
| PLA:QUE+RISLAI   | 2                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PLA:VAL          | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | Major concerns | Very low          |
| AOM:ARI          | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:ARI+LAM      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:ARI+VAL      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:ASE          | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:CAR          | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:LAM          | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| AOM:LAM+OXC      | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:LIT          | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:LIT+OXC      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:LIT+VAL      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| Combination         | Concerns | Suspected | Major Concerns | No Concerns | Major Concerns | Low  |
|---------------------|----------|-----------|----------------|-------------|----------------|------|
| AOM:OLA             | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| AOM:PAL             | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| AOM:QUE             | 0        | No concerns | No concerns | No concerns | No concerns | Low  |
| AOM:RISLAI          | 0        | No concerns | No concerns | No concerns | No concerns | Low  |
| AOM:VAL             | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI:ARI+LAM         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI:ARI+VAL         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI:ASE             | 0        | No concerns | No concerns | No concerns | No concerns | Low  |
| ARI:CAR             | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI:LAM             | 0        | Some concerns | No concerns | Major concerns | No concerns | Very low |
| ARI:LAM+VAL         | 0        | Some concerns | No concerns | Major concerns | No concerns | Very low |
| ARI:LIT             | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI:LIT+OXC         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI:LIT+VAL         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI:OLA             | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI:PLA             | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI:QUE             | 0        | No concerns | No concerns | No concerns | No concerns | Low  |
| ARI:RISLAI          | 0        | No concerns | No concerns | No concerns | No concerns | Low  |
| ARI+LAM:ARI+VAL     | 0        | Some concerns | No concerns | Major concerns | No concerns | Very low |
| ARI+LAM:ASE         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI+LAM:CAR         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI+LAM:LAM+VAL     | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI+LAM:LIT         | 0        | Some concerns | No concerns | Major concerns | No concerns | Very low |
| ARI+LAM:LIT+OXC     | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI+LAM:LIT+VAL     | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI+LAM:OLA         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI+LAM:PAL         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI+LAM:LAM         | 0        | Some concerns | No concerns | Major concerns | No concerns | Very low |
| ARI+LAM:QUE         | 0        | Some concerns | No concerns | Major concerns | No concerns | Very low |
| ARI+LAM:RISLAI      | 0        | No concerns | No concerns | No concerns | No concerns | Low  |
| ARI+LAM:VAL         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| ARI+VAL:ASE         | 0        | No concerns | No concerns | Major concerns | No concerns | Low  |
| Combination          | Concerns | Suspected | Major Concerns | No Concerns | No Concerns | No Concerns | No Concerns | No Concerns | No Concerns | No Concerns |
|----------------------|----------|-----------|----------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| ARI+VAL:CAR          | 0        |            |                | No concerns | No concerns | No concerns | No concerns | No concerns | No concerns | Moderate    |
| ARI+VAL:LAM          | 0        | Some concerns |                | Major concerns | No concerns | No concerns | No concerns | Very low    |
| ARI+VAL:LAM+VAL      | 0        | Some concerns |                | Major concerns | No concerns | No concerns | No concerns | Very low    |
| ARI+VAL:LIT          | 0        |            |                | No concerns | No concerns | No concerns | No concerns | Very low    |
| ARI+VAL:LIT+OXC      | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| ARI+VAL:LIT+VAL      | 0        | Major concerns |                | No concerns | No concerns | No concerns | No concerns | Very low    |
| ARI+VAL:OLA          | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| ARI+VAL:PAL          | 0        | No concerns |                | No concerns | No concerns | No concerns | No concerns | Low         |
| ARI+VAL:PLA          | 0        | Some concerns |                | No concerns | No concerns | Major concerns | No concerns | No concerns | Very low    |
| ARI+VAL:QUE          | 0        | Some concerns |                | No concerns | Major concerns | No concerns | No concerns | Very low    |
| ARI+VAL:RISLAI       | 0        | No concerns |                | No concerns | No concerns | No concerns | No concerns | Moderate    |
| ASE:CAR              | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| ASE:LAM              | 0        | Some concerns |                | No concerns | Major concerns | No concerns | No concerns | Very low    |
| ASE:LAM+VAL          | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Very low    |
| ASE:LIT              | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| ASE:LIT+OXC          | 0        | No concerns |                | No concerns | No concerns | No concerns | No concerns | Low         |
| ASE:LIT+VAL          | 0        | No concerns |                | No concerns | No concerns | No concerns | No concerns | Low         |
| ASE:OLA              | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| ASE:PAL              | 0        | No concerns |                | No concerns | Major concerns | No concerns | No concerns | Low         |
| ASE:QUE              | 0        | No concerns |                | No concerns | Major concerns | No concerns | No concerns | Low         |
| ASE:RISLAI           | 0        | No concerns |                | No concerns | Major concerns | No concerns | No concerns | Low         |
| ASE:VAL              | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| CAR:LAM              | 0        | Some concerns |                | No concerns | Major concerns | No concerns | No concerns | Very low    |
| CAR:LAM+VAL          | 0        | Some concerns |                | No concerns | No concerns | No concerns | No concerns | Low         |
| CAR:LIT+OXC          | 0        | No concerns |                | No concerns | No concerns | No concerns | No concerns | Moderate    |
| CAR:LIT+VAL          | 0        | Major concerns |                | No concerns | No concerns | No concerns | No concerns | Very low    |
| CAR:OLA              | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| CAR:PAL              | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| CAR:PLA              | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| CAR:QUE              | 0        | No concerns |                | No concerns | No concerns | No concerns | No concerns | Moderate    |
| CAR:RISLAI           | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| CAR:VAL              | 0        | No concerns |                | Major concerns | No concerns | No concerns | No concerns | Low         |
| LAM:LIT+OXC          | 0        | Some concerns |                | No concerns | Major concerns | No concerns | No concerns | Very low    |
| Combination        | Concerns | Suspected | No Concerns | Major Concerns | No Concerns | No Concerns | Very Low |
|--------------------|----------|-----------|-------------|----------------|-------------|-------------|----------|
| LAM:LIT+VAL        | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM:OLA            | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LAM:PAL            | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM:QUE            | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM:RISLAI         | 0        | No concerns    | Suspected    | No concerns    | No concerns   | No concerns | No concerns | Moderate |
| LAM:VAL            | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:LIT        | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:LIT+OXC    | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:LIT+VAL    | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:OLA        | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:PAL        | 0        | Some concerns | Suspected    | No concerns    | No concerns   | No concerns | No concerns | Low      |
| LAM+VAL:PLA        | 0        | Some concerns | Suspected    | No concerns    | No concerns   | No concerns | No concerns | Low      |
| LAM+VAL:QUE        | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:RISLAI     | 0        | Some concerns | Suspected    | No concerns    | No concerns   | No concerns | No concerns | Low      |
| LAM+VAL:VAL        | 0        | Some concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LIT:PAL            | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT:QUE            | 0        | No concerns    | Suspected    | No concerns    | No concerns   | No concerns | No concerns | Moderate |
| LIT:RISLAI         | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT+OXC:LIT+VAL    | 0        | Major concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LIT+OXC:OLA        | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT+OXC:PAL        | 0        | No concerns    | Suspected    | No concerns    | No concerns   | No concerns | No concerns | Moderate |
| LIT+OXC:PLA        | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT+OXC:QUE        | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT+OXC:RISLAI     | 0        | No concerns    | Suspected    | No concerns    | No concerns   | No concerns | No concerns | Moderate |
| LIT+OXC:VAL        | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT+OXC:PLA        | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT+OXC:QUE        | 0        | Major concerns | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LIT+OXC:RISLAI     | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| OLA:PAL            | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| OLA:QUE            | 0        | No concerns    | Suspected    | No concerns    | No concerns   | Major concerns | No concerns | Low      |
| OLA:VAL            | 0        | No concerns    | Suspected    | No concerns    | Major concerns | No concerns | No concerns | Low      |
| PAL:QUE            | 0        | No concerns    | Suspected    | No concerns    | No concerns   | No concerns | Low      | Moderate |
|                  | PAL:RISLAI |    |    |    |    |    |    | PAL:VAL |    |    |    |    |    | QUE:RISLAI |    |    |    | QUE:VAL |    |    |    | RISLAI:VAL |    |    |    |    |    |
|------------------|------------|----|----|----|----|----|----|---------|----|----|----|----|----|-------------|----|----|----|---------|----|----|----|-------------|----|----|----|----|----|
|                  | 0          | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low     | 0          | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low     | 0          | Some concerns | Suspected | No concerns | No concerns | No concerns | No concerns | Moderate     | Low     |
|                  | 0          | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low     | 0          | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low     | 0          | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low     |
| Interventions vs placebo | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) |
|--------------------------|------------|------------|------------|------------|------------|------------|
| AOM                      | 1.061 (0.573, 1.962) | 1.028 (0.496, 2.135) | 0.974 (0.468, 2.032) | 1.078 (0.463, 2.467) | 0.998 (0.502, 2.077) | 1.030 (0.517, 2.046) |
| ARI                      | 0.900 (0.417, 1.942) | 0.848 (0.337, 1.956) | 0.921 (0.369, 2.200) | 0.870 (0.319, 2.330) | 0.791 (0.321, 2.030) | 0.884 (0.367, 2.029) |
| ARI+LAM                  | 0.574 (0.315, 1.046) | 0.565 (0.262, 1.119) | 0.556 (0.257, 1.100) | 0.448 (0.180, 1.034) | 0.575 (0.268, 1.167) | 0.557 (0.270, 1.071) |
| ARI+VAL                  | 0.273 (0.076, 0.986) | 0.308 (0.082, 0.976) | 0.296 (0.067, 0.961) | 0.182 (0.031, 0.790) | 0.299 (0.074, 1.008) | 0.322 (0.083, 1.026) |
| ASE                      | 0.385 (0.138, 1.069) | 0.354 (0.103, 0.993) | 0.297 (0.086, 0.897) | 0.331 (0.094, 1.032) | 0.352 (0.115, 1.004) | 0.335 (0.107, 0.910) |
| CAR                      | 2.729 (0.635, 11.735) | 3.016 (0.001, 24.587) | 3.206 (0.802, 24.878) | 3.600 (0.704, 33.562) | 3.178 (0.835, 19.757) | 3.108 (0.800, 30.615) |
| LAM                      | 0.713 (0.547, 0.930) | 0.680 (0.472, 0.922) | 0.670 (0.455, 0.924) | 0.575 (0.359, 0.885) | 0.689 (0.473, 0.940) | 0.664 (0.470, 0.900) |
| LAM+VAL                  | 0.470 (0.278, 0.793) | 0.446 (0.223, 0.811) | 0.433 (0.207, 0.805) | 0.221 (0.072, 0.630) | 0.445 (0.222, 0.848) | 0.428 (0.222, 0.783) |
| LIT                      | 0.791 (0.660, 0.948) | 0.761 (0.597, 0.954) | 0.771 (0.605, 0.951) | 0.697 (0.499, 0.978) | 0.775 (0.598, 0.972) | 0.750 (0.597, 0.928) |
| LIT+OXC                  | 0.294 (0.086, 1.002) | 0.253 (0.054, 0.822) | 0.244 (0.053, 0.810) | 0.184 (0.032, 0.797) | 0.245 (0.055, 0.813) | 0.234 (0.044, 0.776) |
| LIT+VAL                  | 0.741 (0.481, 1.142) | 0.690 (0.389, 1.158) | 0.702 (0.383, 1.188) | 0.629 (0.291, 1.295) | 0.704 (0.382, 1.190) | 0.687 (0.398, 1.103) |
| OLA                      | 0.742 (0.562, 0.979) | 0.712 (0.495, 0.995) | 0.695 (0.482, 0.977) | 0.657 (0.412, 1.016) | 0.708 (0.489, 1.003) | 0.739 (0.516, 1.021) |
| PAL                      | 1.311 (0.796, 2.157) | 1.302 (0.693, 2.361) | 1.727 (0.664, 4.859) | 1.436 (0.693, 2.984) | 1.291 (0.689, 2.387) | 1.323 (0.735, 2.380) |
| QUE                      | 0.480 (0.364, 0.633) | 0.476 (0.324, 0.684) | 0.476 (0.330, 0.685) | 0.437 (0.252, 0.730) | 0.472 (0.327, 0.676) | 0.487 (0.343, 0.676) |
| RISLAI                   | 1.287 (0.857, 1.932) | 1.246 (0.768, 2.001) | 1.288 (0.798, 2.113) | 1.369 (0.793, 2.372) | 1.265 (0.778, 2.090) | 1.348 (0.827, 2.113) |
| VAL                      | 0.848 (0.596, 1.206) | 0.761 (0.467, 1.129) | 0.768 (0.478, 1.146) | 0.737 (0.400, 1.251) | 0.779 (0.471, 1.168) | 0.770 (0.487, 1.125) |
### Sensitivity Analysis

| Interventions vs placebo | RR (95% CI) | Focusing on studies including only BDI | Focusing on studies including only non rapid-cycling BD patients | Focusing on double-blind studies | Focusing on non-enriched studies | Focusing on non-industry sponsorship studies |
|--------------------------|-------------|--------------------------------------|---------------------------------------------------------------|---------------------------------|----------------------------------|---------------------------------------------|
| AOM                      | 1.061 (0.573, 1.962) | 1.020 (0.505, 2.076) | 1.013 (0.508, 2.044) | 1.015 (0.515, 2.003) | 0.979 (0.392, 2.469) | 0.977 (0.390, 2.400) |
| ARI                      | 0.900 (0.417, 1.942) | 0.838 (0.353, 1.923) | 0.774 (0.233, 2.198) | 0.835 (0.380, 1.908) | 0.794 (0.242, 2.374) | 0.802 (0.238, 2.305) |
| ARI+LAM                  | 0.574 (0.315, 1.046) | 0.564 (0.270, 1.132) | 0.588 (0.237, 1.353) | 0.572 (0.290, 1.063) | 0.579 (0.233, 1.449) | 0.596 (0.240, 1.385) |
| ARI+VAL                  | 0.273 (0.076, 0.986) | 0.303 (0.077, 0.992) | 0.369 (0.047, 1.662) | 0.280 (0.067, 0.839) | 0.356 (0.059, 1.689) | 0.401 (0.069, 1.713) |
| ASE                      | 0.385 (0.138, 1.069) | 0.346 (0.113, 0.957) | 0.345 (0.106, 0.921) | 0.350 (0.114, 0.922) | 0.305 (0.049, 1.200) | 0.318 (0.050, 1.202) |
| CAR                      | 2.729 (0.635, 11.735) | 4.128 (0.605, 86.834) | 4.041 (0.656, 84.894) | 3.080 (0.856, 19.051) | 3.321 (0.788, 24.464) | 3.746 (0.691, 49.730) |
| LAM                      | 0.713 (0.547, 0.930) | 0.678 (0.475, 0.922) | 0.686 (0.455, 0.985) | 0.688 (0.495, 0.908) | 0.675 (0.441, 0.993) | 0.693 (0.453, 1.000) |
| LAM+VAL                  | 0.470 (0.278, 0.793) | 0.423 (0.179, 0.913) | 0.437 (0.189, 0.888) | 0.444 (0.232, 0.797) | 0.434 (0.176, 0.920) | 0.448 (0.223, 0.821) |
| LIT                      | 0.791 (0.660, 0.948) | 0.749 (0.583, 0.940) | 0.761 (0.579, 0.976) | 0.760 (0.618, 0.926) | 0.763 (0.595, 0.956) | 0.784 (0.611, 0.986) |
| LIT+OXC                  | 0.294 (0.086, 1.002) | 0.219 (0.021, 1.094) | 0.207 (0.016, 0.967) | 0.242 (0.050, 0.770) | 0.242 (0.052, 0.800) | 0.237 (0.055, 0.803) |
| LIT+VAL                  | 0.741 (0.481, 1.142) | 0.690 (0.383, 1.139) | 0.681 (0.368, 1.237) | 0.654 (0.361, 1.134) | 0.698 (0.383, 1.153) | 0.749 (0.417, 1.222) |
| OLA                      | 0.742 (0.562, 0.979) | 0.705 (0.492, 0.985) | 0.683 (0.468, 0.990) | 0.717 (0.517, 0.971) | 0.715 (0.471, 1.046) | 0.711 (0.465, 1.050) |
| PAL                      | 1.311 (0.796, 2.157) | 1.288 (0.702, 2.367) | 1.282 (0.721, 2.319) | 1.281 (0.725, 2.266) | 1.248 (0.606, 2.695) | 1.231 (0.596, 2.579) |
| QUE                      | 0.480 (0.364, 0.633) | 0.463 (0.311, 0.679) | 0.468 (0.308, 0.688) | 0.471 (0.338, 0.657) | 0.473 (0.298, 0.712) | 0.471 (0.305, 0.698) |
| RISLAI                   | 1.287 (0.857, 1.932) | 1.240 (0.774, 1.956) | 1.222 (0.794, 1.908) | 1.253 (0.794, 1.940) | 1.203 (0.658, 2.212) | 1.184 (0.656, 2.149) |
| VAL                      | 0.848 (0.596, 1.206) | 0.765 (0.458, 1.121) | 0.781 (0.462, 1.260) | 0.703 (0.444, 1.055) | 0.767 (0.466, 1.133) | 0.855 (0.507, 1.278) |
1.3. Recurrence/relapse rate of manic/hypomanic/mixed episodes (25 RCTs, 6438 patients)
League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|       | AOM       | ARI       | ARI+LAM   | ARI+VAL   | ASE       | CAR       | LAM       | LAM+VAL   |
|-------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
|       | 0.726     | 0.590     | 0.586     | 0.146     | **0.340** | 0.199     | 0.989     | 0.386     |
|       | (0.288, 1.832) | (0.242, 1.439) | (0.121, 2.848) | (0.017, 1.280) | **(0.173, 0.668)** | (0.621, 6.431) | (0.020, 4.931) | **(0.010, 0.989)** |
|       | 0.560     | 1.004     | 0.557     | 0.014     | 1.000     | 0.772     | 1.714     | **0.386** |
|       | (0.288, 1.875) | (0.299, 1.051) | (0.165, 3.496) | (0.038, 1.900) | 1.383     | (0.371, 1.604) | (0.149, 5.088) | **(0.149, 0.999)** |
|       | 0.872     | 0.761     | 1.000     | 1.004     | 0.872     | 1.397     | 1.488     | 0.601     |
|       | (0.453, 1.679) | (0.368, 1.573) | (0.288, 1.501) | (0.288, 1.501) | 1.049     | (0.463, 2.374) | (0.296, 6.533) | **(0.129, 0.999)** |
|       | 0.511     | 0.726     | 0.772     | 0.511     | 0.511     | 0.866     | 0.872     | 0.352     |
|       | (0.286, 1.039) | (0.322, 1.031) | (0.216, 2.732) | (0.288, 1.900) | 1.291     | (0.728, 2.787) | (0.339, 1.862) | **(0.129, 0.866)** |
|       | 0.545     | 2.822     | 1.703     | 0.545     | 1.703     | 1.479     | 0.930     | **0.352** |
|       | (0.417, 1.617) | (0.298, 1.031) | (0.473, 1.875) | (0.473, 1.875) | 1.299     | (0.728, 2.787) | (0.192, 1.862) | **(0.129, 0.999)** |
|       | 0.472     | 4.440     | 1.488     | 1.488     | 1.560     | 1.999     | 0.872     | 0.511     |
|       | (0.243, 0.920) | (0.489, 1.714) | (0.322, 1.031) | (0.322, 1.031) | 1.999     | (0.621, 2.372) | (0.288, 1.875) | (0.288, 1.875) |
|       | 0.302     | 2.523     | 0.872     | 0.545     | 0.872     | 0.866     | 0.930     | 0.511     |
|       | (0.166, 1.560) | (0.285, 0.993) | (0.489, 1.714) | (0.489, 1.714) | 1.560     | (0.621, 2.372) | (0.288, 1.875) | (0.288, 1.875) |

The results indicate statistical significance.
|          |          |          |          |          |          |          |          |          |          |          |          |
|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|          |          |          |          |          |          |          |          |          |          |          |          |
| 3.833    | 1.891    | LIT      | 1.793    | 1.359    | 1.557    | 0.912    | 0.973    | 1.465    | 0.843    | 0.540    | 0.301    |
| (0.480,  | (1.147,  |          | (0.611,  | (0.935,  | (1.173,  | (0.593,  | (0.729,  | (1.013,  | (0.657,  | (0.445,  | (0.101,  |
| 30.597)  | 3.117)   |          | 5.265)   | 1.975)   | 2.065)   | 1.403)   | 1.299)   | 2.120)   | 1.083)   | 0.655)   | (0.899)  |
|          |          |          |          |          |          |          |          |          |          |          |          |
| 1.793    | LIT+OXC  | 0.758    | 0.868    | 0.509    | 0.543    | 0.817    | 0.470    | 0.621    | 0.397    | 0.263    | 0.599    |
| (0.611,  |          | (0.242,  | (0.285,  | (0.159,  | (0.178,  | (0.262,  | (0.156,  | (0.433,  | (0.263,  | (0.101,  | (0.899)  |
| 5.265)   |          | 2.370)   | 2.644)   | 1.622)   | 1.655)   | 2.552)   | 1.421)   | 0.889)   | (0.263,  | (0.101,  | (0.899)  |
|          |          |          |          |          |          |          |          |          | 0.599)   |          |          |
| 1.333    | LIT+V    | 1.145    | 0.671    | 0.716    | 1.078    | 0.642    | 1.044    | 0.376    | 0.347    | 0.265    | 0.453    |
| (0.900,  | AL       | (0.721,  |          |          |          |          |          | (0.781)  |          |          |          |
| 1.975)   |          | 1.820)   |          |          |          |          |          |          |          |          |          |
| 1.690    |          | 0.586    | 0.625    | 0.941    | 0.542    | 1.506    | 0.867    | 0.555    | 0.368    | 0.268    | 0.507    |
| (1.120,  |          | (0.367,  | (0.439,  | (0.631,  | (0.376,  | (1.010,  | (0.601,  | (0.435,  | (0.268,  | (0.101,  | (0.707)  |
| 2.550)   |          | 0.936)   | 0.891)   | 1.404)   | 0.781)   | 2.247)   | 1.251)   | (0.707)  | (0.268,  | (0.101,  |          |
|          |          |          |          |          |          |          |          |          | 0.507)   |          |          |
|          |          |          |          |          |          |          |          |          |          |          |          |
| 0.928    |          |          |          |          |          | 0.896    |          |          |          |          |          |
| (0.644,  |          |          |          |          |          | (0.478,  |          |          |          |          |          |
| 1.337)   |          |          |          |          |          | 1.679)   |          |          |          |          |          |
|          |          |          |          |          |          |          |          |          |          |          |          |
| 0.806    |          |          |          |          |          |          | 0.612    |          |          |          |          |
| (0.192,  |          |          |          |          |          | (0.423,  | (0.423,  |          |          |          |          |
| 3.381)   |          |          |          |          |          | 0.886)   | 0.423)   |          |          |          |          |
|          |          |          |          |          |          |          |          |          |          |          |          |
| 0.302    |          |          |          |          |          |          |          | 0.612    |          |          |          |
| (0.166,  |          |          |          |          |          |          | (0.423,  | (0.423,  |          |          |          |
| 0.550)   |          |          |          |          |          |          | 0.886)   | 0.423)   |          |          |          |
|          | 0.416    |          | 0.523    |          | 0.369    |          | 0.535    |          | 0.369    |          |          |
| (0.206,  |          | (0.422,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  |          |          |
| 0.529)   |          | 0.648)   | 0.514)   | 0.684)   | 0.514)   | 0.684)   | 0.514)   | 0.684)   | 0.514)   |          |          |
|          | 0.208    |          | 0.523    |          | 0.369    |          | 0.535    |          | 0.369    |          |          |
| (0.082,  |          | (0.422,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  |          |          |
| 0.529)   |          | 0.648)   | 0.514)   | 0.684)   | 0.514)   | 0.684)   | 0.514)   | 0.684)   | 0.514)   |          |          |
|          | 0.864    |          | 0.523    |          | 0.369    |          | 0.535    |          | 0.369    |          |          |
| (0.621,  |          | (0.422,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  |          |          |
| 1.202)   |          | 0.648)   | 0.514)   | 0.684)   | 0.514)   | 0.684)   | 0.514)   | 0.684)   | 0.514)   |          |          |
|          | 0.907    |          | 0.612    |          | 0.369    |          | 0.535    |          | 0.369    |          |          |
| (0.697,  |          | (0.423,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  | (0.265,  |          |          |
| 1.180)   |          | 0.886)   | 0.514)   | 0.684)   | 0.514)   | 0.684)   | 0.514)   | 0.684)   | 0.514)   |          |          |
|          |          |          |          |          |          |          |          |          |          | 0.790    |          |
|          |          |          |          |          |          |          |          |          | (0.485,  |          |          |
|          |          |          |          |          |          |          |          |          | 1.286)   |          |          |
|          |          |          |          |          |          |          |          |          |          |          | PLA      |
|          |          |          |          |          |          |          |          |          |          |          |          |
### Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|-----------------------------------|--------------------------|---------------------------------------------------|
|                                   |                          | Q        | df | p               |
| 0.01                              | Low                      | 13.398   | 10 | 0.202           |

#### Inconsistency

|                   | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures | Ratio of risk ratios | P value |
|-------------------|-----------------|--------------------|----------------------|------------------------|----------------------|---------|
| LAM vs LIT        | 1.649 (1.166, 2.333) | 1.891 (1.147, 3.117) | 1.453 (0.898, 2.351) | 1.302 (0.650, 2.605) | 0.457                |
| LAM vs PLA        | 0.890 (0.650, 1.219) | 0.864 (0.621, 1.202) | 1.189 (0.425, 3.327) | 0.727 (0.247, 2.142) | 0.563                |
| LIT vs LIT+VAL    | 1.359 (0.935, 1.975) | 1.333 (0.900, 1.975) | 1.637 (0.482, 5.562) | 0.815 (0.225, 2.944) | 0.754                |
| LIT vs OLA        | 1.557 (1.173, 2.065) | 1.690 (1.120, 2.550) | 1.446 (0.980, 2.134) | 1.168 (0.663, 2.058) | 0.590                |
| LIT vs QUE        | 0.973 (0.729, 1.299) | 0.928 (0.644, 1.337) | 1.052 (0.656, 1.688) | 0.882 (0.485, 1.603) | 0.681                |
| LIT vs VAL        | 0.843 (0.657, 1.083) | 0.907 (0.697, 1.180) | 0.436 (0.197, 0.965) | 2.079 (0.900, 4.802) | 0.086                |
| LIT vs PLA        | 0.540 (0.445, 0.655) | 0.523 (0.422, 0.648) | 0.620 (0.396, 0.972) | 0.843 (0.512, 1.388) | 0.502                |
| LIT+VAL vs VAL    | 0.621 (0.433, 0.889) | 0.612 (0.423, 0.886) | 0.790 (0.167, 3.747) | 0.775 (0.156, 3.836) | 0.754                |
| OLA vs RISLAI     | 0.941 (0.631, 1.404) | 0.896 (0.478, 1.679) | 0.974 (0.580, 1.635) | 0.920 (0.407, 2.077) | 0.841                |
| OLA vs PLA        | 0.347 (0.265, 0.453) | 0.369 (0.265, 0.514) | 0.308 (0.195, 0.486) | 1.199 (0.683, 2.105) | 0.528                |
| QUE vs PLA        | 0.555 (0.435, 0.707) | 0.535 (0.418, 0.684) | 2.085 (0.479, 9.078) | 0.256 (0.058, 1.140) | 0.074                |
| RISLAI vs PLA     | 0.368 (0.268, 0.507) | 0.369 (0.268, 0.509) | 0.308 (0.025, 3.819) | 1.200 (0.095, 15.194) | 0.888                |
| VAL vs PLA        | 0.640 (0.477, 0.857) | 0.790 (0.485, 1.286) | 0.568 (0.394, 0.819) | 1.390 (0.755, 2.558) | 0.290                |
|        | Rank 1  | Rank 2  | Rank 3  | Rank 4  | Rank 5  | Rank 6  | Rank 7  | Rank 8  | Rank 9  | Rank 10 | Rank 11 | Rank 12 | Rank 13 | Rank 14 | Rank 15 | Rank 16 | Rank 17 |
|--------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| AOM    | 0.102   | 0.194   | 0.194   | 0.144   | 0.103   | 0.080   | 0.066   | 0.044   | 0.026   | 0.017   | 0.011   | 0.008   | 0.006   | 0.004   | 0.001   | 0.000   | 0.000   |
| ARI    | 0.034   | 0.083   | 0.098   | 0.094   | 0.096   | 0.093   | 0.096   | 0.092   | 0.079   | 0.053   | 0.046   | 0.046   | 0.045   | 0.025   | 0.013   | 0.007   | 0.001   |
| ARI+LAM| 0.006   | 0.017   | 0.034   | 0.042   | 0.053   | 0.064   | 0.092   | 0.093   | 0.096   | 0.079   | 0.081   | 0.093   | 0.108   | 0.077   | 0.035   | 0.026   | 0.005   |
| ARI+VAL| 0.039   | 0.050   | 0.045   | 0.038   | 0.036   | 0.041   | 0.043   | 0.043   | 0.038   | 0.039   | 0.042   | 0.050   | 0.065   | 0.075   | 0.078   | 0.194   | 0.084   |
| ASE    | 0.488   | 0.225   | 0.107   | 0.052   | 0.036   | 0.030   | 0.021   | 0.016   | 0.007   | 0.005   | 0.003   | 0.003   | 0.004   | 0.002   | 0.000   | 0.001   | 0.000   |
| CAR    | 0.001   | 0.003   | 0.002   | 0.002   | 0.002   | 0.003   | 0.004   | 0.005   | 0.008   | 0.007   | 0.011   | 0.013   | 0.019   | 0.030   | 0.034   | 0.064   | 0.795   |
| LAM    | 0.000   | 0.000   | 0.000   | 0.000   | 0.000   | 0.000   | 0.001   | 0.001   | 0.002   | 0.006   | 0.017   | 0.046   | 0.116   | 0.302   | 0.345   | 0.143   | 0.021   |
| LAM+VAL| 0.049   | 0.076   | 0.070   | 0.065   | 0.054   | 0.061   | 0.070   | 0.068   | 0.059   | 0.054   | 0.053   | 0.064   | 0.070   | 0.069   | 0.044   | 0.063   | 0.014   |
| LIT    | 0.000   | 0.000   | 0.000   | 0.000   | 0.004   | 0.014   | 0.048   | 0.124   | 0.216   | 0.246   | 0.197   | 0.107   | 0.035   | 0.008   | 0.001   | 0.000   | 0.000   |
| LIT+OXC| 0.249   | 0.196   | 0.121   | 0.076   | 0.065   | 0.056   | 0.050   | 0.046   | 0.030   | 0.025   | 0.020   | 0.020   | 0.019   | 0.014   | 0.008   | 0.005   | 0.002   |
| LIT+VAL| 0.011   | 0.043   | 0.089   | 0.116   | 0.133   | 0.153   | 0.153   | 0.123   | 0.077   | 0.044   | 0.027   | 0.017   | 0.008   | 0.005   | 0.001   | 0.000   | 0.000   |
| LIT+OXC| 0.001   | 0.003   | 0.007   | 0.013   | 0.020   | 0.032   | 0.053   | 0.082   | 0.103   | 0.118   | 0.126   | 0.137   | 0.137   | 0.100   | 0.051   | 0.018   | 0.003   |
| PAL    | 0.000   | 0.000   | 0.000   | 0.002   | 0.005   | 0.015   | 0.034   | 0.063   | 0.119   | 0.166   | 0.221   | 0.210   | 0.122   | 0.037   | 0.006   | 0.000   |
| PLA    | 0.000   | 0.000   | 0.000   | 0.000   | 0.000   | 0.000   | 0.000   | 0.000   | 0.000   | 0.001   | 0.003   | 0.026   | 0.096   | 0.328   | 0.472   | 0.075   |         |
| SUCRA              |       |
|--------------------|-------|
| ASE                | 0.86  |
| AOM                | 0.78  |
| LIT+OXC            | 0.77  |
| OLA                | 0.75  |
| RISLAI             | 0.74  |
| LIT+VAL            | 0.70  |
| ARI                | 0.61  |
| ARI+VAL            | 0.48  |
| ARI+LAM            | 0.46  |
| LAM+VAL            | 0.46  |
| LIT                | 0.45  |
| PAL                | 0.42  |
| QUE                | 0.37  |
| VAL                | 0.32  |
| LAM                | 0.16  |
| PLA                | 0.10  |
| CAR                | 0.07  |
| Comparison     | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|----------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| AOM:PLA        | 1                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Moderate         |
| AOM:ARI        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:ARI+LAM    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:ARI+VAL    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Very low         |
| AOM:ASE        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:CAR        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Very low         |
| AOM:LAM        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:LAM+VAL    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:LIT        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Very low         |
| AOM:LIT+OXC    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:LIT+VAL    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:LIT+VAL    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Very low         |
| AOM:OLI        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:QUE        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:QUE        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Very low         |
| AOM:RISLAI     | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:RISLAI     | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:VAL        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Moderate         |
| AOM:ARI-LAM    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:ARI+VAL    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:ASE        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:CAR        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:LAM        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:LAM+VAL    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:LIT        | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Very low         |
| AOM:LIT+OXC    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| AOM:LIT+VAL    | 0                 | No concerns       | Suspected      | No concerns  | No concerns | No concerns   | No concerns  | Low              |
| Configuration       | Score | Concerns | Concerns | Concerns | Concerns | Concerns | Score |
|--------------------|-------|----------|----------|----------|----------|----------|-------|
| AOM:OLA            | 0     | No       | Suspected| No       | No       | No       | Low   |
| AOM:PAL            | 0     | No       | Suspected| No       | No       | No       | Low   |
| AOM:QUE            | 0     | No       | Suspected| No       | No       | No       | Low   |
| AOM:RISLAI         | 0     | No       | Suspected| No       | No       | No       | Low   |
| AOM:VAL            | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:ARI+LAM        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:ARI+VAL        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:ASE            | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:CAR            | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM            | 0     | Some     | Suspected| No       | No       | No       | Very low |
| ARI:LAM+VAL        | 0     | Some     | Suspected| No       | No       | No       | Very low |
| ARI:LIT            | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LIT+OXC        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LIT+VAL        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM+LAM+VAL    | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM:ASE        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM:CAR        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM:LAM+VAL    | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM:LIT        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM:LIT+OXC    | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM:LIT+VAL    | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM:OLA        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM:PAL        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI:LAM:PLA        | 0     | Some     | Suspected| No       | No       | Major    | No     |
| ARI:LAM:QUE        | 0     | Some     | Suspected| No       | Major    | No       | No     |
| ARI:LAM:RISLAI     | 0     | No       |Suspected | No       | No       | No       | Low   |
| ARI:LAM:VAL        | 0     | No       |Suspected | No       | No       | No       | Low   |
| ARI+LAM:ASE        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+LAM:CAR        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+LAM:LAM+VAL    | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+LAM:LIT        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+LAM:LIT+OXC    | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+LAM:LIT+VAL    | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+LAM:OLA        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+LAM:PAL        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+LAM:PLA        | 0     | Some     | Suspected| No       | Major    | No       | No     |
| ARI+LAM:QUE        | 0     | Some     | Suspected| No       | Major    | No       | No     |
| ARI+LAM:RISLAI     | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+LAM:VAL        | 0     | No       | Suspected| No       | No       | No       | Low   |
| ARI+VAL:ASE        | 0     | No       | Suspected| No       | No       | No       | Low   |
| Combination          | Score | Concerns 1 | Concerns 2 | Concerns 3 | Concerns 4 | Concerns 5 | Concerns 6 | Risk Level |
|----------------------|-------|------------|------------|------------|------------|------------|------------|------------|
| ARI+VAL:CAR          | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ARI+VAL:LAM          | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| ARI+VAL:LAM+VAL      | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| ARI+VAL:LIT          | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| ARI+VAL:LIT+OXC      | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ARI+VAL:LIT+VAL      | 0     | Major concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| ARI+VAL:OLA          | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ARI+VAL:PAL          | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ARI+VAL:PLA          | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| ARI+VAL:QUE          | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| ARI+VAL:RISLAI       | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:CAR              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:LAM              | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:LAM+VAL          | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| ASE:LIT              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:LIT+OXC          | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:LIT+VAL          | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:OLA              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:PAL              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:QUE              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:RISLAI           | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| ASE:VAL              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Moderate   |
| CAR:LAM              | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| CAR:LAM+VAL          | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| CAR:LIT+OXC          | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| CAR:LIT+VAL          | 0     | Major concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| CAR:OLA              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| CAR:PAL              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| CAR:PLA              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| CAR:QUE              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| CAR:RISLAI           | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| CAR:VAL              | 0     | No concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Low        |
| LAM:LIT+OXC          | 0     | Some concerns| Suspected  | No concerns| Major concerns| No concerns| No concerns| Very low   |
| Combination          | Concerns    | Suspected | No concerns | Major concerns | No concerns | Very low | Low       |
|----------------------|-------------|-----------|-------------|----------------|-------------|----------|-----------|
| LAM:LIT+VAL          | 0           | Some concerns | No concerns | No concerns | No concerns | No concerns | Low       |
| LAM:OLA              | 0           | No concerns | Suspected   | No concerns | No concerns | No concerns | Moderate  |
| LAM:PAL              | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM:QUE              | 0           | Some concerns | No concerns | No concerns | No concerns | No concerns | Low       |
| LAM:RISLAI           | 0           | No concerns | Suspected   | No concerns | No concerns | No concerns | Moderate  |
| LAM:VAL              | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM+VAL:LIT          | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM+VAL:LIT+OXC      | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM+VAL:LIT+VAL      | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM+VAL:OLA          | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM+VAL:PAL          | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM+VAL:PLA          | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM+VAL:QUE          | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM+VAL:RISLAI       | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM+VAL:VAL          | 0           | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LIT:VAL              | 0           | No concerns | Suspected   | No concerns | Major concerns | No concerns | Low       |
| LIT:RISLAI           | 0           | No concerns | Suspected   | No concerns | Major concerns | No concerns | Low       |
| LIT+OXC:LIT+VAL      | 0           | Major concerns | Suspected   | No concerns | Major concerns | No concerns | Very low  |
| LIT+OXC:OLA          | 0           | No concerns | Suspected   | No concerns | Major concerns | No concerns | Low       |
| LIT+OXC:PAL          | 0           | No concerns | Suspected   | No concerns | Major concerns | No concerns | Low       |
| LIT+OXC:PLA          | 0           | No concerns | Suspected   | No concerns | No concerns   | No concerns | Moderate  |
| LIT+OXC:QUE          | 0           | No concerns | Suspected   | No concerns | Major concerns | No concerns | Low       |
| LIT+OXC:RISLAI       | 0           | No concerns | Suspected   | No concerns | Major concerns | No concerns | Low       |
| LIT+OXC:VAL          | 0           | No concerns | Suspected   | No concerns | Major concerns | No concerns | Low       |
| LIT+RISLAI           | 0           | No concerns | Suspected   | No concerns | No concerns   | No concerns | Low       |
| LIT+VAL:OLA          | 0           | No concerns | Suspected   | No concerns | No concerns   | No concerns | Moderate  |
| LIT+VAL:PAL          | 0           | No concerns | Suspected   | No concerns | No concerns   | No concerns | Moderate  |
| LIT+VAL:PLA          | 0           | No concerns | Suspected   | No concerns | No concerns   | No concerns | Moderate  |
| LIT+VAL:QUE          | 0           | Some concerns | Suspected   | No concerns | Major concerns | No concerns | Very low  |
| LIT+VAL:RISLAI       | 0           | No concerns | Suspected   | No concerns | Major concerns | No concerns | Low       |
| OLA:PAL              | 0           | No concerns | Suspected   | No concerns | No concerns   | No concerns | Moderate  |
| OLA:QUE              | 0           | No concerns | Suspected   | No concerns | No concerns   | No concerns | Moderate  |
| OLA:VAL              | 0           | No concerns | Suspected   | No concerns | No concerns   | No concerns | Moderate  |
| PAL:QUE              | 0           | No concerns | Suspected   | No concerns | Major concerns | No concerns | Low       |
| Category   | Concerns     | Suspected | Major Concerns | No Concerns | No Concerns | No Concerns | No Concerns | Level |
|------------|--------------|-----------|----------------|-------------|-------------|-------------|-------------|-------|
| PAL:RISLAI | 0 No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | No concerns | Low   |
| PAL:VAL    | 0 No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | No concerns | Low   |
| QUE:RISLAI | 0 No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | No concerns | Low   |
| QUE:VAL    | 0 Some concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | No concerns | Very low |
| RISLAI:VAL | 0 No concerns | Suspected | No concerns    | No concerns   | No concerns | No concerns | No concerns | Moderate |
## Meta-regression analysis

| Interventions vs placebo | Primary analysis | Publication year | Duration of study | Number of total patients | Percent female | Mean age |
|--------------------------|------------------|------------------|-------------------|-------------------------|---------------|---------|
| Heterogeneity SD         | 0.100            | 0.145            | 0.079             | 0.092                   | 0.141         | 0.162   |
| Relative change in the variance \( \beta \), median (95% CI) | +45% (-0.529, 0.383) | -21% (-0.422, 0.077) | -8% (-0.535, 0.724) | +41% (-0.669, 0.381) | +62% |

| Interventions vs placebo | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) |
|--------------------------|------------|------------|------------|------------|------------|------------|
| AOM                      | 0.302 (0.166, 0.550) | 0.310 (0.139, 0.629) | 0.251 (0.120, 0.480) | 0.293 (0.144, 0.554) | 0.285 (0.133, 0.568) | 0.295 (0.135, 0.580) |
| ARI                      | 0.416 (0.206, 0.843) | 0.390 (0.158, 0.847) | 0.472 (0.209, 1.011) | 0.382 (0.172, 0.792) | 0.338 (0.132, 0.933) | 0.386 (0.155, 0.859) |
| ARI+LAM                  | 0.513 (0.265, 0.993) | 0.515 (0.233, 1.128) | 0.517 (0.254, 1.059) | 0.532 (0.250, 1.095) | 0.529 (0.220, 1.160) | 0.519 (0.223, 1.165) |
| ARI+VAL                  | 0.516 (0.119, 2.228) | 0.614 (0.133, 2.859) | 0.659 (0.135, 2.604) | 0.668 (0.144, 2.992) | 0.660 (0.144, 2.911) | 0.633 (0.139, 2.866) |
| ASE                      | 0.208 (0.082, 0.529) | 0.196 (0.059, 0.521) | 0.141 (0.046, 0.346) | 0.187 (0.066, 0.472) | 0.187 (0.056, 0.486) | 0.197 (0.061, 0.495) |
| CAR                      | 2.069 (0.257,16.663) | 3.169 (0.476, 71.665) | 3.723 (0.506, 192.481) | 3.670 (0.505, 37.420) | 3.001 (0.490, 68.518) | 3.310 (0.486, 84.125) |
| LAM                      | 0.890 (0.650, 1.219) | 0.856 (0.583, 1.254) | 0.851 (0.600, 1.208) | 0.884 (0.625, 1.245) | 0.881 (0.592, 1.300) | 0.876 (0.583, 1.285) |
| LAM+VAL                  | 0.543 (0.189, 1.560) | 0.469 (0.137, 1.426) | 0.475 (0.144, 1.273) | 0.475 (0.148, 1.426) | 0.471 (0.135, 1.427) | 0.480 (0.138, 1.446) |
| LIT                      | 0.540 (0.445, 0.655) | 0.528 (0.408, 0.686) | 0.554 (0.440, 0.687) | 0.593 (0.455, 0.755) | 0.557 (0.410, 0.730) | 0.529 (0.410, 0.693) |
| LIT+OXC                  | 0.301 (0.101, 0.899) | 0.254 (0.069, 0.810) | 0.276 (0.083, 0.774) | 0.298 (0.082, 0.888) | 0.273 (0.071, 0.803) | 0.251 (0.066, 0.789) |
| LIT+VAL                  | 0.397 (0.263, 0.599) | 0.380 (0.215, 0.669) | 0.394 (0.243, 0.620) | 0.429 (0.251, 0.696) | 0.403 (0.217, 0.697) | 0.385 (0.210, 0.668) |
| OLA                      | 0.347 (0.265, 0.453) | 0.341 (0.239, 0.479) | 0.333 (0.243, 0.455) | 0.366 (0.259, 0.500) | 0.340 (0.238, 0.483) | 0.328 (0.222, 0.480) |
| PAL                      | 0.592 (0.403, 0.870) | 0.605 (0.345, 1.035) | 1.220 (0.516, 2.903) | 0.590 (0.355, 0.949) | 0.608 (0.333, 1.042) | 0.574 (0.320, 1.025) |
| QUE                      | 0.555 (0.435, 0.707) | 0.592 (0.412, 0.877) | 0.621 (0.459, 0.848) | 0.717 (0.467, 1.083) | 0.591 (0.416, 0.869) | 0.565 (0.396, 0.867) |
| RISLAI                   | 0.368 (0.268, 0.507) | 0.373 (0.237, 0.559) | 0.423 (0.278, 0.617) | 0.376 (0.256, 0.550) | 0.389 (0.224, 0.615) | 0.349 (0.211, 0.554) |
| VAL                      | 0.640 (0.477, 0.857) | 0.611 (0.409, 0.910) | 0.624 (0.447, 0.859) | 0.684 (0.464, 0.980) | 0.652 (0.411, 0.961) | 0.612 (0.409, 0.924) |
| Sensitivity analysis | Primary analysis | Focusing on studies including only BDI | Focusing on studies including only non rapid-cycling BD patients | Focusing on double-blind studies | Focusing on non-enriched studies | Focusing on non-industry sponsorship studies |
|---------------------|------------------|--------------------------------------|---------------------------------------------------------------|--------------------------------|-------------------------------|-----------------------------------------------|
| Heterogeneity SD    | 0.100            | 0.125                                | 0.113                                                         | 0.147                          | 0.121                         | 0.106                                          |
| Relative change in the variance | +25%             | +13%                                 | +47%                                                          | +21%                           | +6%                           |
| Interventions vs placebo | RR (95%CI)      | RR (95%CI)                           | RR (95%CI)                                                  | RR (95%CI)                     | RR (95%CI)                     | RR (95%CI)                                     |
| AOM                 | 0.302 (0.166, 0.550) | 0.289 (0.142, 0.561)                | 0.284 (0.139, 0.562)                                         | 0.293 (0.140, 0.568)           | 0.276 (0.102, 0.643)          | 0.272 (0.086, 0.635)                           |
| ARI                 | 0.416 (0.206, 0.843) | 0.396 (0.176, 0.823)                | 0.380 (0.117, 1.002)                                         | 0.387 (0.165, 0.837)           | 0.361 (0.117, 1.000)          | 0.375 (0.119, 0.983)                           |
| ARI+LAM             | 0.513 (0.265, 0.993) | 0.518 (0.234, 1.095)                | 0.521 (0.198, 1.435)                                         | 0.519 (0.229, 1.117)           | 0.522 (0.175, 1.683)          | 0.540 (0.196, 1.412)                           |
| ARI+VAL             | 0.516 (0.119, 2.228) | 0.646 (0.150, 2.768)                | 0.833 (0.110, 7.103)                                         | 0.613 (0.139, 2.873)           | 0.888 (0.132, 6.632)          | 0.863 (0.102, 7.334)                           |
| ASE                 | 0.208 (0.082, 0.529) | 0.191 (0.058, 0.482)                | 0.185 (0.061, 0.450)                                         | 0.188 (0.059, 0.480)           | 0.178 (0.028, 0.647)          | 0.166 (0.029, 0.574)                           |
| CAR                 | 2.069 (0.257, 16.663) | 5.014 (0.365, 3.491.896)            | 4.527 (0.468, 199.059)                                        | 3.293 (0.460, 109.969)         | 3.460 (0.505, 168.865)        | 5.232 (0.298, 327.438)                          |
| LAM                 | 0.890 (0.650, 1.219) | 0.858 (0.594, 1.239)                | 0.830 (0.511, 1.312)                                         | 0.853 (0.576, 1.259)           | 0.841 (0.516, 1.324)          | 0.845 (0.525, 1.317)                           |
| LAM+VAL             | 0.543 (0.189, 1.560) | 0.413 (0.068, 1.929)                | 0.408 (0.068, 1.862)                                         | 0.479 (0.144, 1.459)           | 0.421 (0.069, 1.912)          | 0.448 (0.136, 1.306)                           |
| LIT                 | 0.540 (0.445, 0.655) | 0.520 (0.409, 0.670)                | 0.518 (0.385, 0.704)                                         | 0.531 (0.419, 0.686)           | 0.552 (0.418, 0.711)          | 0.522 (0.396, 0.694)                           |
| LIT+OXC             | 0.301 (0.101, 0.899) | 0.220 (0.027, 0.980)                | 0.208 (0.025, 0.921)                                         | 0.261 (0.075, 0.792)           | 0.271 (0.067, 0.790)          | 0.241 (0.067, 0.697)                           |
| LIT+VAL             | 0.397 (0.263, 0.599) | 0.375 (0.220, 0.636)                | 0.371 (0.185, 0.711)                                         | 0.384 (0.192, 0.719)           | 0.401 (0.230, 0.671)          | 0.383 (0.212, 0.654)                           |
| OLA                 | 0.347 (0.265, 0.453) | 0.335 (0.242, 0.467)                | 0.335 (0.224, 0.499)                                         | 0.337 (0.239, 0.476)           | 0.335 (0.226, 0.496)          | 0.333 (0.216, 0.498)                           |
| PAL                 | 0.592 (0.403, 0.870) | 0.587 (0.344, 0.963)                | 0.578 (0.348, 0.981)                                         | 0.586 (0.333, 1.003)           | 0.573 (0.295, 1.084)          | 0.571 (0.300, 1.037)                           |
| QUE                 | 0.555 (0.435, 0.707) | 0.530 (0.374, 0.808)                | 0.551 (0.372, 0.858)                                         | 0.573 (0.406, 0.856)           | 0.561 (0.375, 0.871)          | 0.548 (0.374, 0.839)                           |
| RISLAI              | 0.368 (0.268, 0.507) | 0.361 (0.242, 0.534)                | 0.367 (0.243, 0.535)                                         | 0.364 (0.238, 0.547)           | 0.360 (0.210, 0.588)          | 0.355 (0.212, 0.575)                           |
| VAL                 | 0.640 (0.477, 0.857) | 0.611 (0.419, 0.892)                | 0.600 (0.376, 0.960)                                         | 0.613 (0.405, 0.916)           | 0.643 (0.427, 0.925)          | 0.617 (0.411, 0.928)                           |
1.4. All-cause discontinuation (29 RCTs, 6988 patients)
League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|                | AOM      | 0.750 (0.456, 1.232) | 0.964 (0.556, 1.672) | 0.897 (0.429, 1.873) | 1.614 (0.858, 3.038) | 0.739 (0.453, 1.207) | 0.882 (0.453, 1.350) | 0.833 (0.453, 1.532) | 0.868 (0.453, 1.293) | 0.778 (0.453, 1.846) | 0.998 (0.606, 1.644) | 1.059 (0.692, 1.620) | 0.813 (0.491, 1.344) | 1.105 (0.712, 1.714) | 0.924 (0.592, 1.443) | 0.910 (0.590, 1.406) | 0.726 (0.501, 1.054) |
|----------------|----------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
|                | ARI      | 1.286 (0.763, 2.167) | 1.196 (0.584, 2.446) | 2.153 (1.172, 3.953) | 0.986 (0.624, 1.558) | 1.177 (0.799, 1.734) | 1.110 (0.619, 1.656) | 1.157 (0.809, 2.419) | 1.037 (0.445, 2.124) | 1.331 (0.958, 2.081) | 1.412 (0.985, 2.881) | 1.084 (0.818, 1.857) | 1.232 (0.816, 1.807) | 1.214 (0.697, 1.345) | 0.969 (0.679, 1.345) |
|                | ARI+LAM  | 0.930 (0.440, 1.967) | 1.674 (0.871, 3.217) | 0.767 (0.462, 1.298) | 0.915 (0.645, 1.511) | 0.864 (0.592, 1.933) | 0.900 (0.592, 1.933) | 0.807 (0.437, 1.725) | 1.035 (0.699, 1.430) | 1.098 (0.699, 1.430) | 0.843 (0.497, 1.539) | 1.146 (0.720, 1.848) | 0.958 (0.599, 1.488) | 0.753 (0.502, 1.131) |
|                | ARI+VAL  | 1.800 (0.796, 4.072) | 0.825 (0.414, 1.640) | 0.984 (0.507, 1.909) | 0.929 (0.420, 2.053) | 0.968 (0.517, 2.180) | 0.868 (0.322, 2.335) | 1.113 (0.570, 2.286) | 1.181 (0.610, 2.528) | 0.906 (0.441, 1.863) | 1.233 (0.630, 2.265) | 1.030 (0.522, 2.034) | 1.015 (0.429, 1.841) | 0.810 (0.429, 1.530) |
|                | ASE      | 0.458 (0.251, 0.837) | 0.547 (0.315, 0.949) | 0.516 (0.255, 1.042) | 0.538 (0.316, 0.914) | 0.482 (0.190, 1.138) | 0.618 (0.336, 1.138) | 0.656 (0.378, 1.138) | 0.503 (0.273, 0.930) | 0.685 (0.390, 1.201) | 0.572 (0.325, 1.009) | 0.564 (0.323, 0.986) | 0.450 (0.270, 0.750) |
|                | CAR      | 1.194 (0.828, 1.722) | 1.126 (0.637, 1.992) | 1.174 (0.883, 1.560) | 1.052 (0.464, 2.052) | 1.350 (0.988, 2.056) | 1.432 (0.998, 2.175) | 1.099 (0.690, 1.750) | 1.495 (1.021, 2.188) | 1.250 (0.839, 1.862) | 1.231 (0.872, 1.739) | 0.983 (0.714, 1.352) | 0.983 (0.714, 1.352) |
|                | LAM      | 0.915 (0.645, 1.298) | 0.944 (0.610, 1.460) | 0.983 (0.781, 1.238) | 0.882 (0.396, 1.653) | 1.131 (0.774, 1.597) | 1.200 (0.902, 1.733) | 0.921 (0.620, 1.369) | 1.252 (0.921, 1.703) | 1.047 (0.761, 1.441) | 1.032 (0.771, 1.380) | 0.823 (0.670, 1.011) |
|                | LAM+VAL  | 0.944 (0.610, 1.460) | 1.042 (0.636, 1.707) | 0.934 (0.375, 2.326) | 1.199 (0.672, 2.138) | 1.272 (0.755, 2.143) | 0.976 (0.541, 1.760) | 1.327 (0.778, 2.263) | 1.109 (0.646, 1.847) | 1.093 (0.647, 1.847) | 0.872 (0.538, 1.414) |
|          |          |          |          |          |          |          |          |          |          |
|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| LIT      | 0.897    | LIT+OXC  | 1.283    | 1.361    | 1.045    | 1.420    | 1.188    | 1.170    | 0.934    |
|          | (0.416,  | (0.416,  | (0.562,  | (0.613,  | (0.446,  | (0.633,  | (0.525,  | (0.530,  | (0.428,  |
|          | 1.930)   | 1.930)   | 2.931)   | 3.025)   | 2.445)   | 3.185)   | 2.686)   | 2.581)   | 2.037)   |
|          |          |          |          |          |          |          |          |          |          |
| LIT+V    | 1.089    | LIT+V    | 1.061    | 0.814    | 1.107    | 0.926    | 0.912    | 0.728    | 0.686    |
|          | (0.779,  | VAL      | (0.729,  | (0.506,  | (0.747,  | (0.614,  | (0.672,  | (0.522,  | (0.558,  |
|          | 1.522)   |          | 1.544)   | 1.309)   | 1.642)   | 1.395)   | 1.238)   | 1.015)   | 0.843)   |
|          |          |          |          |          |          |          |          |          |          |
| VAL      | 1.261    | VAL      | 0.767    | 1.044    | 0.872    | 0.860    | 0.860    | 0.657    | 0.657    |
|          | (0.891,  |          | (0.516,  | (1.417)  | (1.166)  | (0.646,  | (1.144)  | (0.637,  | (0.657,  |
|          | 1.786)   |          | 1.141)   |          |          | 1.144)   |          | 1.254)   | 0.830)   |
|          |          |          |          |          |          |          |          |          |          |
| PAL      | 1.346    | PAL      | 1.360    | 1.137    | 1.120    | 0.894    | 0.894    | 0.657    | 0.657    |
|          | (0.945,  |          | (0.901,  | (1.727)  | (1.746,  | (0.637,  | (0.637,  | (0.657,  | (0.657,  |
|          | 1.918)   |          | 2.052)   |          | 1.682)   | 1.254)   |          | 1.254)   | 0.830)   |
|          |          |          |          |          |          |          |          |          |          |
| QUE      | 1.346    | QUE      | 0.689    | 0.836    | 0.824    | 0.985    | 0.786    | 0.798    | 0.798    |
|          | (0.945,  |          | (0.461,  | (0.596,  | (0.604,  | (0.709,  | (0.615,  | (0.638,  | (0.638,  |
|          | 1.918)   |          | 1.029)   | 1.172)   | 1.123)   | 1.369)   | 1.005)   | 0.999)   | 0.999)   |
|          |          |          |          |          |          |          |          |          |          |
| RISLAI   | 1.015    | RISLAI   | 1.073    | 0.865    | 0.719    | 0.894    | 0.748    | 0.821    | 0.798    |
|          | (0.560,  |          | (0.876,  | (0.621,  | (0.710,  | (0.637,  | (0.580,  | (0.576,  | (0.638,  |
|          | 1.841)   |          | 1.314)   | 1.206)   | 0.978)   | 1.254)   | 0.830)   | 1.171)   | 0.999)   |
|          |          |          |          |          |          |          |          |          |          |
| PLA      | 0.726    | PLA      | 0.450    | 0.834    | 0.833    | 0.719    | 0.649    | 0.748    | 0.821    |
|          | (0.501,  |          | (0.270,  | (0.671,  | (0.710,  | (0.560,  | (0.507,  | (0.580,  | (0.576,  |
|          | 1.054)   |          | 0.750)   | 1.035)   | 0.978)   | 1.254)   | 0.830)   | 1.171)   | 0.999)   |
|          |          |          |          |          |          |          |          |          |          |
|          | 0.969    |          |          |          |          |          |          |          |          |
|          | (0.697,  |          |          |          |          |          |          |          |          |
|          | 1.345)   |          |          |          |          |          |          |          |          |
Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|-----------------------------------------------------|
|                                  |                          | Q     | df  | p               |
| 0.026                            | Low                      | 4.183 | 10  | 0.939           |

### Inconsistency

|                  | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures | Ratio of risk ratios | P value |
|------------------|-----------------|--------------------|----------------------|-----------------------|----------------------|---------|
| LAM vs LIT       | 0.983 (0.781, 1.238) | 0.995 (0.713, 1.388) | 0.973 (0.708, 1.338) | 1.023 (0.645, 1.621) | 0.924                |
| LAM vs PLA       | 0.823 (0.670, 1.011) | 0.834 (0.671, 1.035) | 0.729 (0.374, 1.424) | 1.143 (0.566, 2.309) | 0.709                |
| LIT vs LIT+VAL   | 1.150 (0.846, 1.564) | 1.089 (0.779, 1.522) | 1.536 (0.712, 3.312) | 0.709 (0.307, 1.640) | 0.422                |
| LIT vs OLA       | 1.220 (0.977, 1.524) | 1.261 (0.891, 1.786) | 1.193 (0.894, 1.593) | 1.057 (0.673, 1.662) | 0.809                |
| LIT vs QUE       | 1.274 (0.989, 1.640) | 1.346 (0.945, 1.918) | 1.202 (0.837, 1.726) | 1.120 (0.675, 1.859) | 0.660                |
| LIT vs VAL       | 1.049 (0.864, 1.274) | 1.073 (0.876, 1.314) | 0.806 (0.404, 1.605) | 1.332 (0.650, 2.733) | 0.434                |
| LIT vs PLA       | 0.837 (0.725, 0.966) | 0.833 (0.710, 0.978) | 0.852 (0.618, 1.177) | 0.978 (0.682, 1.401) | 0.902                |
| LIT+VAL vs VAL   | 0.912 (0.672, 1.238) | 0.865 (0.621, 1.206) | 1.230 (0.558, 2.711) | 0.704 (0.299, 1.658) | 0.422                |
| OLA vs RISLAI    | 0.872 (0.653, 1.166) | 0.689 (0.461, 1.029) | 1.129 (0.742, 1.716) | 0.610 (0.342, 1.091) | 0.096                |
| OLA vs PLA       | 0.686 (0.558, 0.843) | 0.719 (0.560, 0.924) | 0.621 (0.432, 0.892) | 1.159 (0.746, 1.800) | 0.512                |
| QUE vs PLA       | 0.657 (0.520, 0.830) | 0.649 (0.507, 0.830) | 0.741 (0.350, 1.568) | 0.875 (0.398, 1.926) | 0.741                |
| RISLAI vs PLA    | 0.786 (0.615, 1.005) | 0.748 (0.580, 0.965) | 1.515 (0.603, 3.805) | 0.494 (0.190, 1.283) | 0.147                |
| VAL vs PLA       | 0.798 (0.638, 0.999) | 0.821 (0.576, 1.171) | 0.783 (0.586, 1.046) | 1.049 (0.664, 1.658) | 0.837                |
### Rank probabilities

|       | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 | Rank 11 | Rank 12 | Rank 13 | Rank 14 | Rank 15 | Rank 16 | Rank 17 |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| AOM   | 0.036  | 0.120  | 0.118  | 0.102  | 0.093  | 0.078  | 0.074  | 0.064  | 0.053  | 0.046  | 0.047  | 0.040  | 0.041  | 0.028  | 0.024  | 0.028  | 0.014  |
| ARI   | 0.001  | 0.006  | 0.011  | 0.015  | 0.021  | 0.027  | 0.034  | 0.037  | 0.041  | 0.047  | 0.056  | 0.075  | 0.095  | 0.111  | 0.126  | 0.151  | 0.147  |
| ARI+LAM | 0.025  | 0.081  | 0.087  | 0.080  | 0.085  | 0.084  | 0.077  | 0.068  | 0.062  | 0.057  | 0.055  | 0.051  | 0.046  | 0.043  | 0.038  | 0.037  | 0.024  |
| ARI+VAL | 0.041  | 0.090  | 0.066  | 0.055  | 0.052  | 0.047  | 0.046  | 0.043  | 0.044  | 0.039  | 0.041  | 0.045  | 0.047  | 0.052  | 0.061  | 0.090  | 0.141  |
| ASE   | 0.753  | 0.119  | 0.047  | 0.027  | 0.014  | 0.011  | 0.008  | 0.006  | 0.004  | 0.003  | 0.001  | 0.001  | 0.001  | 0.001  | 0.001  | 0.001  | 0.001  |
| CAR   | 0.000  | 0.001  | 0.002  | 0.006  | 0.011  | 0.013  | 0.021  | 0.023  | 0.029  | 0.038  | 0.046  | 0.074  | 0.095  | 0.114  | 0.147  | 0.193  | 0.186  |
| LAM   | 0.000  | 0.001  | 0.003  | 0.013  | 0.029  | 0.053  | 0.083  | 0.110  | 0.132  | 0.144  | 0.147  | 0.124  | 0.087  | 0.048  | 0.020  | 0.005  | 0.001  |
| LAM+VAL | 0.013  | 0.046  | 0.041  | 0.049  | 0.049  | 0.049  | 0.051  | 0.049  | 0.047  | 0.048  | 0.054  | 0.061  | 0.074  | 0.073  | 0.081  | 0.096  | 0.120  |
| LIT   | 0.000  | 0.000  | 0.000  | 0.002  | 0.007  | 0.025  | 0.052  | 0.106  | 0.152  | 0.193  | 0.187  | 0.152  | 0.082  | 0.035  | 0.008  | 0.001  | 0.000  |
| LIT+OXC | 0.054  | 0.096  | 0.054  | 0.044  | 0.043  | 0.041  | 0.035  | 0.034  | 0.033  | 0.032  | 0.032  | 0.038  | 0.040  | 0.046  | 0.056  | 0.092  | 0.231  |
| LIT+VAL | 0.021  | 0.090  | 0.102  | 0.119  | 0.102  | 0.102  | 0.088  | 0.082  | 0.086  | 0.054  | 0.044  | 0.042  | 0.030  | 0.024  | 0.018  | 0.015  | 0.005  |
| OLA   | 0.014  | 0.106  | 0.173  | 0.183  | 0.165  | 0.125  | 0.087  | 0.058  | 0.034  | 0.025  | 0.014  | 0.009  | 0.004  | 0.001  | 0.001  | 0.000  | 0.000  |
| PAL   | 0.004  | 0.016  | 0.023  | 0.033  | 0.035  | 0.055  | 0.057  | 0.053  | 0.056  | 0.059  | 0.068  | 0.084  | 0.096  | 0.098  | 0.095  | 0.096  | 0.073  |
| QUE   | 0.035  | 0.197  | 0.210  | 0.170  | 0.133  | 0.086  | 0.061  | 0.036  | 0.027  | 0.019  | 0.010  | 0.007  | 0.005  | 0.003  | 0.001  | 0.000  | 0.000  |
| RISLAI | 0.004  | 0.026  | 0.046  | 0.065  | 0.094  | 0.111  | 0.107  | 0.102  | 0.092  | 0.076  | 0.078  | 0.066  | 0.056  | 0.036  | 0.023  | 0.012  | 0.006  |
| VAL   | 0.001  | 0.005  | 0.018  | 0.037  | 0.067  | 0.093  | 0.119  | 0.130  | 0.132  | 0.113  | 0.097  | 0.074  | 0.056  | 0.035  | 0.016  | 0.006  | 0.002  |
| PLA   | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.002  | 0.007  | 0.019  | 0.056  | 0.146  | 0.252  | 0.286  | 0.183  | 0.050  |
| Drug Combination | SUCRA |
|------------------|-------|
| LIT+VAL          | 0.87  |
| OLA              | 0.82  |
| ASE              | 0.67  |
| QUE              | 0.62  |
| ARI+LAM          | 0.61  |
| RISLAI           | 0.54  |
| AOM              | 0.53  |
| VAL              | 0.51  |
| ARI+VAL          | 0.50  |
| LAM              | 0.47  |
| LIT              | 0.46  |
| LAM+VAL          | 0.40  |
| LIT+OXC          | 0.40  |
| PAL              | 0.37  |
| ARI              | 0.37  |
| CAR              | 0.26  |
| PLA              | 0.10  |
| Comparison         | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|--------------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| AOM:PLA            | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| ARI:PLA            | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| ARI+LAM:LAM        | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| ARI+VAL:VAL        | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| ASE:PLA            | 1                 | No concerns       | Suspected      | No concerns  | No concerns    | No concerns    | No concerns  | Very low         |
| CAR:LIT            | 3                 | Major concerns    | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LAM+VAL:LAM+VAL    | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LAM:LIT            | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LAM:PLA            | 3                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LIT:LIT+OXC        | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| LIT:LIT+VAL        | 6                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LIT:PLA            | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LIT:QUE            | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LIT:VAL            | 3                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| LIT+VAL:LIT+VAL    | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LIT:PLA            | 2                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| OLA:RISEI          | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| OLA:RISLAI         | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| PAL:PLA            | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| PL:RISEI           | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| PLA:RISEI          | 2                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| PLA:VAL            | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:ARI            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:ARI+LAM        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:ARI+VAL        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:ASE            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:CAR            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:LAM            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:LAM+VAL        | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| AOM:LIT            | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:LIT+OXC        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:LIT+VAL        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| Combination          | Score | No concerns | Suspected | Major concerns | No concerns | No concerns | Concern | Level     |
|----------------------|-------|-------------|-----------|----------------|-------------|-------------|---------|-----------|
| AOM:OLA              | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| AOM:PAL              | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| AOM:QUE              | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| AOMRISLAI            | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| AOM:VAL              | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:ARI+LAM          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:ARI+VAL          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:ASE              | 0     | No concerns | Suspected | No concerns    | No concerns    | No concerns | No concerns | Moderate  |
| ARI:CAR              | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:LAM              | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:LAM+VAL          | 0     | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low  |
| ARI:LIT              | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:LIT+OXC          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:LIT+VAL          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:OLA              | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:QUE              | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI:RISLAI           | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:ARI+VAL      | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:ASE          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:CAR          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:LAM+VAL      | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:LIT          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:LIT+OXC      | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:LIT+VAL      | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:OLA          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:PAL          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:PLA          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:QUE          | 0     | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low  |
| ARI+LAMRISLAI        | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:VAL          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| ARI+VAL:ASE          | 0     | No concerns | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low       |
| Combination       | Concerns          | Suspected | Other Concerns | Major Concerns | Other Concerns | Other Concerns | Other Concerns | Other Concerns | Other Concerns |
|-------------------|-------------------|-----------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| ARI+VAL:CAR       | 0                 | Some      | No             | Major          | No             | No             | No             | Very low       |
| ARI+VAL:LAM       | 0                 | Some      | No             | Major          | No             | No             | No             | Very low       |
| ARI+VAL:LAM+VAL   | 0                 | Some      | No             | Major          | No             | No             | No             | Very low       |
| ARI+VAL:LIT       | 0                 | Some      | No             | Major          | No             | No             | No             | Very low       |
| ARI+VAL:LIT+OXC   | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ARI+VAL:LIT+VAL   | 0                 | Major     | Suspected      | No             | Major          | No             | No             | Very low       |
| ARI+VAL:OLA       | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ARI+VAL:PAL       | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ARI+VAL:PLA       | 0                 | Some      | Suspected      | No             | Major          | No             | No             | Very low       |
| ARI+VAL:QUE       | 0                 | Some      | Suspected      | No             | Major          | No             | No             | Very low       |
| ARI+VAL:RISLAI    | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:CAR           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:LAM           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:LAM+VAL       | 0                 | Some      | Suspected      | No             | Major          | No             | No             | Very low       |
| ASE:LIT           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:LIT+OXC       | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:LIT+VAL       | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:OLA           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:PAL           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:QUE           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:RISLAI        | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| ASE:VAL           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| CAR:LAM           | 0                 | Some      | Suspected      | No             | Major          | No             | No             | Very low       |
| CAR:LAM+VAL       | 0                 | Some      | Suspected      | No             | Major          | No             | No             | Very low       |
| CAR:LIT+OXC       | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| CAR:LIT+VAL       | 0                 | Major     | Suspected      | No             | Major          | No             | No             | Very low       |
| CAR:OLA           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| CAR:PAL           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| CAR:PLA           | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| CAR:QUE           | 0                 | Some      | Suspected      | No             | Major          | No             | No             | Very low       |
| CAR:RISLAI        | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| CAR:VAL           | 0                 | Major     | Suspected      | No             | Major          | No             | No             | Very low       |
| LAM:LIT+OXC       | 0                 | No        | Suspected      | No             | Major          | No             | No             | Low            |
| Combination            | Concerns   | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
|------------------------|------------|-----------|-------------|----------------|-------------|-------------|----------|
| LAM:LIT+VAL            | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM:OLA                | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LAM:PAL                | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LAM:QUE                | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM:RISLAI             | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LAM:VAL                | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:LIT            | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:LIT+OXC        | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:LIT+VAL        | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:OLA            | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:PLA            | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:QUE            | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:RISLAI         | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LAM+VAL:VAL            | 0          | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| LIT:PAL                | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT:QUE                | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT:RISLAI             | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:LIT+VAL        | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:OLA            | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:PLA            | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:QUE            | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:RISLAI         | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:VAL            | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:OLA            | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:PLA            | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:QUE            | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:RISLAI         | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:VAL            | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| LIT+OXC:OLA            | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| PAL:VAL                | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| PAL:QUE                | 0          | No concerns | Suspected   | No concerns    | Major concerns | No concerns | Low      |
| A1       | B1       | C1       | D1       | E1       | F1       | G1       | H1       |
|----------|----------|----------|----------|----------|----------|----------|----------|
| PAL:RISLAI | 0        | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| PAL:VAL   | 0        | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| QUE:RISLAI | 0       | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| QUE:VAL   | 0        | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| RISLAI:VAL | 0       | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
### Meta-regression analysis

|                        | Primary analysis | Publication year | Duration of study | Number of total patients | Percent female | Mean age |
|------------------------|------------------|------------------|-------------------|--------------------------|----------------|----------|
| **Heterogeneity SD**   | 0.161            | 0.156            | 0.151             | 0.177                    | 0.127          | 0.175    |
| **Relative change in the variance** $\beta$, median (95% CI) |                   |                  |                   |                          |                |          |
| AOM                    | 0.651 (0.520, 0.830) | 0.569, 0.965) | 0.539, 0.830) | 0.565, 1.196) | 0.534, 1.063) | 0.519, 1.043) |
| CAR                    | 0.519, 0.965) | 0.533, 0.985) | 0.539, 0.830) | 0.565, 1.196) | 0.534, 1.063) | 0.519, 1.043) |
| LAM                    | 0.477, 0.839) | 0.519, 0.965) | 0.539, 0.830) | 0.565, 1.196) | 0.534, 1.063) | 0.519, 1.043) |
| **Interventions vs placebo** | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** |
| AOM                    | 0.726 (0.501, 1.054) | 0.636 (0.423, 0.953) | 0.681 (0.464, 1.013) | 0.724 (0.475, 1.100) | 0.726 (0.509, 1.010) | 0.702 (0.462, 1.067) |
| ARI                    | 0.969 (0.697, 1.345) | 0.931 (0.654, 1.308) | 1.056 (0.712, 1.510) | 0.961 (0.653, 1.426) | 0.838 (0.614, 1.197) | 0.924 (0.618, 1.354) |
| ARI+LAM                | 0.753 (0.502, 1.131) | 0.772 (0.518, 1.161) | 0.745 (0.496, 1.115) | 0.770 (0.490, 1.212) | 0.817 (0.552, 1.142) | 0.762 (0.493, 1.177) |
| ARI+VAL                | 0.810 (0.429, 1.530) | 0.864 (0.450, 1.687) | 0.839 (0.441, 1.568) | 0.855 (0.433, 1.673) | 0.924 (0.488, 1.682) | 0.824 (0.420, 1.631) |
| ASE                    | 0.450 (0.270, 0.750) | 0.385 (0.222, 0.656) | 0.389 (0.224, 0.672) | 0.443 (0.253, 0.768) | 0.462 (0.274, 0.750) | 0.444 (0.251, 0.759) |
| CAR                    | 0.983 (0.714, 1.352) | 1.043 (0.759, 1.438) | 1.023 (0.731, 1.403) | 1.019 (0.712, 1.438) | 1.117 (0.797, 1.509) | 1.000 (0.709, 1.936) |
| LAM                    | 0.823 (0.670, 1.011) | 0.843 (0.700, 1.007) | 0.811 (0.672, 0.972) | 0.840 (0.683, 1.017) | 0.889 (0.738, 1.026) | 0.828 (0.675, 1.006) |
| LAM+VAL                | 0.872 (0.538, 1.414) | 0.882 (0.545, 1.430) | 0.846 (0.510, 1.357) | 0.879 (0.516, 1.481) | 0.928 (0.588, 1.442) | 0.867 (0.508, 1.445) |
| LIT                    | 0.837 (0.725, 0.966) | 0.872 (0.757, 1.004) | 0.851 (0.741, 0.968) | 0.857 (0.726, 0.995) | 0.919 (0.788, 1.045) | 0.838 (0.724, 0.967) |
| LIT+OXC                | 0.934 (0.428, 2.037) | 0.906 (0.410, 1.984) | 0.887 (0.395, 1.990) | 0.893 (0.386, 1.975) | 0.947 (0.436, 2.031) | 0.875 (0.390, 1.945) |
| LIT+VAL                | 0.728 (0.522, 1.015) | 0.756 (0.534, 1.063) | 0.736 (0.521, 1.017) | 0.744 (0.499, 1.083) | 0.805 (0.575, 1.077) | 0.720 (0.494, 1.053) |
| OLA                    | 0.686 (0.558, 0.843) | 0.673 (0.539, 0.830) | 0.682 (0.549, 0.834) | 0.694 (0.535, 0.877) | 0.718 (0.581, 0.854) | 0.659 (0.511, 0.827) |
| PAL                    | 0.894 (0.637, 1.254) | 0.821 (0.565, 1.196) | 1.203 (0.669, 1.962) | 0.897 (0.600, 1.343) | 0.948 (0.689, 1.291) | 0.857 (0.582, 1.264) |
| QUE                    | 0.657 (0.520, 0.830) | 0.622 (0.483, 0.798) | 0.660 (0.519, 0.836) | 0.691 (0.497, 0.952) | 0.680 (0.548, 0.840) | 0.638 (0.477, 0.839) |
| RISLAI                 | 0.786 (0.615, 1.005) | 0.736 (0.569, 0.965) | 0.822 (0.630, 1.057) | 0.792 (0.594, 1.053) | 0.854 (0.664, 1.076) | 0.731 (0.533, 0.985) |
| VAL                    | 0.798 (0.638, 0.999) | 0.829 (0.651, 1.038) | 0.800 (0.632, 0.992) | 0.817 (0.620, 1.043) | 0.884 (0.697, 1.074) | 0.788 (0.611, 1.006) |
## Sensitivity analysis

|                          | Primary analysis | Focusing on studies including only BDI | Focusing on studies including only non rapid-cycling BD patients | Focusing on double-blind studies | Focusing on non-enriched studies | Focusing on non-industry sponsorship studies |
|--------------------------|------------------|---------------------------------------|---------------------------------------------------------------|---------------------------------|----------------------------------|---------------------------------------------|
| **Heterogeneity SD**     | 0.161            | 0.157                                 | 0.152                                                         | 0.171                           | 0.147                            | 0.166                                       |
| **Relative change in the variance** | -2%              | -6%                                   | 6%                                                            | -9%                             | +3%                              |                                             |
| **Interventions vs placebo** | **RR (95%CI)**   |                                       |                                                               |                                 |                                 |                                             |
| AOM                      | 0.726 (0.501, 1.054) | 0.721 (0.487, 1.063) | 0.724 (0.492, 1.056) | 0.723 (0.478, 1.091) | 0.718 (0.468, 1.098) | 0.720 (0.461, 1.132) |
| ARI                      | 0.969 (0.697, 1.345) | 0.970 (0.676, 1.372) | 0.965 (0.673, 1.388) | 0.971 (0.649, 1.413) | 0.966 (0.672, 1.350) | 0.965 (0.657, 1.403) |
| ARI+LAM                  | 0.753 (0.502, 1.131) | 0.775 (0.509, 1.170) | 0.783 (0.500, 1.203) | 0.768 (0.492, 1.197) | 0.793 (0.515, 1.189) | 0.777 (0.491, 1.247) |
| ARI+VAL                  | 0.810 (0.429, 1.530) | 0.860 (0.438, 1.650) | 0.877 (0.375, 2.014) | 0.835 (0.430, 1.650) | 0.882 (0.390, 1.993) | 0.881 (0.373, 2.047) |
| ASE                      | **0.450 (0.270, 0.750)** | **0.444 (0.253, 0.734)** | **0.442 (0.258, 0.729)** | **0.443 (0.250, 0.752)** | **0.436 (0.223, 0.823)** | **0.436 (0.217, 0.824)** |
| CAR                      | 0.983 (0.714, 1.352) | 1.052 (0.715, 1.532) | 1.049 (0.717, 1.527) | 0.988 (0.689, 1.406) | 1.038 (0.754, 1.427) | 1.034 (0.721, 1.470) |
| LAM                      | 0.823 (0.670, 1.011) | 0.845 (0.694, 1.008) | 0.851 (0.697, 1.021) | 0.836 (0.689, 1.099) | 0.856 (0.704, 1.024) | 0.847 (0.685, 1.032) |
| LAM+VAL                  | 0.872 (0.538, 1.414) | 0.864 (0.475, 1.552) | 0.871 (0.483, 1.570) | 0.875 (0.518, 1.454) | 0.882 (0.491, 1.548) | 0.883 (0.523, 1.463) |
| LIT                      | **0.837 (0.725, 0.966)** | **0.853 (0.742, 0.976)** | **0.849 (0.735, 0.972)** | **0.841 (0.723, 0.968)** | **0.865 (0.756, 0.983)** | **0.846 (0.728, 0.975)** |
| LIT+OXC                  | 0.934 (0.428, 2.037) | 0.832 (0.283, 2.304) | 0.834 (0.282, 2.264) | 0.887 (0.387, 1.984) | 0.902 (0.410, 1.991) | 0.887 (0.394, 1.965) |
| LIT+VAL                  | 0.728 (0.522, 1.015) | 0.741 (0.521, 1.060) | 0.736 (0.509, 1.047) | 0.732 (0.493, 1.068) | 0.752 (0.535, 1.032) | 0.735 (0.502, 1.050) |
| OLA                      | **0.686 (0.558, 0.843)** | **0.693 (0.550, 0.848)** | **0.689 (0.548, 0.848)** | **0.685 (0.540, 0.856)** | **0.708 (0.561, 0.869)** | **0.700 (0.538, 0.877)** |
| PAL                      | 0.894 (0.637, 1.254) | 0.891 (0.621, 1.267) | 0.894 (0.621, 1.258) | 0.893 (0.614, 1.337) | 0.893 (0.622, 1.278) | 0.895 (0.603, 1.331) |
| QUE                      | **0.657 (0.520, 0.830)** | **0.649 (0.505, 0.837)** | **0.659 (0.505, 0.851)** | **0.656 (0.502, 0.852)** | **0.658 (0.511, 0.850)** | **0.654 (0.499, 0.865)** |
| RISLAI                   | 0.786 (0.615, 1.005) | 0.784 (0.605, 1.014) | 0.783 (0.608, 1.017) | 0.784 (0.596, 1.023) | 0.777 (0.588, 1.023) | 0.779 (0.576, 1.046) |
| VAL                      | **0.798 (0.638, 0.999)** | 0.816 (0.635, 1.030) | 0.816 (0.627, 1.022) | 0.801 (0.616, 1.019) | 0.824 (0.654, 1.012) | 0.809 (0.628, 1.033) |
1.5. Discontinuation due to adverse event (21 RCTs, 6107 patients)
## League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

| AOM | 1.096 (0.055, 21.942) | 8.156 (0.641, 103.804) | 19.292 (2.011, 185.045) | 2.524 (0.230, 27.735) | 12.682 (1.150, 139.826) | 3.128 (0.361, 27.105) | 1.870 (0.116, 30.054) | 1.917 (0.178, 20.606) | 3.859 (0.427, 34.848) | 5.751 (0.470, 70.337) | 6.026 (0.686, 52.963) | 3.914 (0.355, 43.216) | 6.266 (0.555, 70.732) | 7.000 (0.847, 57.876) |
|-----|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| ARI | 7.439 (0.578, 95.679) | 17.595 (1.813, 170.784) | 11.568 (1.037, 128.960) | 2.853 (0.325, 25.028) | 1.705 (0.105, 27.677) | 1.749 (0.161, 19.009) | 3.520 (0.385, 32.175) | 5.246 (0.424, 64.845) | 5.496 (0.618, 48.906) | 3.570 (0.320, 39.857) | 5.716 (0.501, 65.229) | 6.385 (0.762, 53.464) |
| ARI+LAM | 2.366 (0.463, 12.078) | 1.555 (0.670, 3.612) | 0.384 (0.095, 1.554) | 0.229 (0.024, 2.149) | 0.235 (0.042, 1.303) | 0.473 (0.109, 2.063) | 0.705 (0.100, 4.974) | 0.739 (0.168, 3.246) | 0.480 (0.081, 2.856) | 0.768 (0.130, 4.557) | 0.858 (0.208, 3.541) |
| ASE | 0.131 (0.033, 0.525) | 0.657 (0.163, 2.655) | 0.162 (0.064, 0.408) | 0.097 (0.013, 0.698) | 0.099 (0.026, 0.384) | 0.200 (0.073, 0.552) | 0.298 (0.062, 1.429) | 0.312 (0.120, 0.811) | 0.203 (0.050, 0.821) | 0.325 (0.077, 1.365) | 0.363 (0.162, 0.812) |
| CAR | 5.025 (1.092, 23.120) | 1.239 (0.438, 3.508) | 0.741 (0.097, 5.658) | 0.760 (0.181, 3.190) | 1.529 (0.486, 4.807) | 2.279 (0.393, 13.217) | 2.388 (0.726, 7.854) | 1.551 (0.332, 7.246) | 2.483 (0.546, 11.292) | 2.773 (0.894, 8.609) |
| LAM | 1.555 (0.670, 3.612) | 0.247 (0.081, 0.753) | 0.147 (0.019, 1.172) | 0.151 (0.034, 0.672) | 0.304 (0.091, 1.018) | 0.453 (0.078, 2.642) | 0.475 (0.141, 1.604) | 0.309 (0.064, 1.486) | 0.494 (0.103, 2.370) | 0.552 (0.177, 1.725) |
| LIT | 0.213 (0.060, 0.757) | 0.598 (0.104, 3.428) | 0.613 (0.228, 1.647) | 1.234 (0.765, 1.991) | 1.839 (0.446, 7.583) | 1.927 (1.080, 3.437) | 1.251 (0.401, 3.903) | 1.203 (0.666, 6.023) | 2.238 (1.430, 3.502) |
| LIT+OX | 0.598 (0.104, 3.428) | 1.026 (0.138, 7.629) | 2.064 (0.337, 12.627) | 3.076 (0.325, 29.160) | 3.223 (0.512, 20.296) | 2.094 (0.260, 16.832) | 3.352 (0.425, 26.417) | 3.744 (0.617, 22.721) |
|                | LIT+VAL | OL A   | P AL   | QUE    | RISLAI | VAL    | PLA    |
|----------------|---------|--------|--------|--------|--------|--------|--------|
| 0.545 (0.196, 1.519) | 2.013 (0.671, 6.033) | 2.999 (0.533, 16.874) | 3.143 (1.000, 9.877) | 2.041 (0.452, 9.210) | 3.268 (1.088, 9.817) | 3.651 (1.234, 10.801) |
| 1.360 (0.819, 2.260) | 1.490 (0.340, 6.540) | 1.562 (0.754, 3.235) | 1.014 (0.335, 3.071) | 1.624 (0.489, 5.392) | 1.814 (0.979, 3.361) |
| 1.586 (0.742, 3.387) | OLA     | PAL    | QUE    |        | RISLAI |        |        |
| 1.008 (0.284, 3.581) |         |        |        |        | 1.601 (0.329, 7.794) | 1.788 (0.571, 5.605) |
| 2.003 (0.666, 6.023) | 2.750 (0.853, 8.862) |        |        |        |        | VAL    |        |
| 0.363 (0.162, 0.812) |         |        |        |        |        | 1.117 (0.340, 3.666) | PLA    |
| 7.000 (0.847, 57.876) | 6.385 (0.762, 53.464) | 0.898 (0.236, 3.412) | 2.179 (1.322, 3.592) | 4.426 (1.057, 18.541) | 1.217 (0.317, 4.668) | 1.111 (0.645, 1.912) | 1.981 (0.476, 8.256) | PLA |

**Evaluation of heterogeneity and inconsistency**

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|---------------------------------------------------|
| 0.034                           | Low to moderate          | Q = 5.635, df = 8, p = 0.699                      |
## Inconsistency

|                          | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures | Ratio of risk ratios | P value       |
|--------------------------|-----------------|--------------------|----------------------|------------------------|---------------------|--------------|
| **LAM vs LIT**           | 0.247 (0.081, 0.753) | 0.213 (0.060, 0.757) | 0.410 (0.039, 4.297) |                        | 0.519 (0.036, 7.490) | 0.630        |
| **LAM vs PLA**           | 0.552 (0.177, 1.725) | 0.898 (0.236, 3.412) | 0.149 (0.017, 1.332) |                        | 6.013 (0.463, 78.038) | 0.170        |
| **LIT vs LIT+VAL**       | 0.613 (0.228, 1.647) | 0.545 (0.196, 1.519) | 2.915 (0.069, 123.100) |                        | 0.187 (0.004, 9.067) | 0.397        |
| **LIT vs OLA**           | 1.234 (0.765, 1.991) | 1.360 (0.819, 2.260) | 0.564 (0.134, 2.375) |                        | 2.410 (0.525, 11.065) | 0.258        |
| **LIT vs QUE**           | 1.927 (1.080, 3.437) | 1.586 (0.742, 3.387) | 2.525 (1.033, 6.174) |                        | 0.628 (0.194, 2.029) | 0.437        |
| **LIT vs PLA**           | 2.238 (1.430, 3.502) | 2.179 (1.322, 3.592) | 2.494 (0.912, 6.824) |                        | 0.874 (0.284, 2.688) | 0.814        |
| **LIT+VAL vs VAL**       | 3.268 (1.088, 9.817) | 2.750 (0.853, 8.862) | 12.084 (0.482, 302.869) |                        | 0.228 (0.007, 7.008) | 0.397        |
| **OLA vs RISLAI**        | 1.014 (0.335, 3.071) | 1.008 (0.284, 3.581) | 1.036 (0.106, 10.103) |                        | 0.973 (0.072, 13.184) | 0.983        |
| **OLA vs PLA**           | 1.814 (0.979, 3.361) | 4.426 (1.057, 18.541) | 1.481 (0.748, 2.932) |                        | 2.990 (0.612, 14.617) | 0.176        |
| **QUE vs PLA**           | 1.162 (0.696, 1.937) | 1.111 (0.645, 1.912) | 1.648 (0.360, 7.552) |                        | 0.674 (0.134, 3.395) | 0.633        |
| **RISLAI vs PLA**        | 1.788 (0.571, 5.605) | 1.981 (0.476, 8.256) | 1.489 (0.221, 10.021) |                        | 1.330 (0.123, 14.392) | 0.814        |
|        | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 | Rank 11 | Rank 12 | Rank 13 | Rank 14 | Rank 15 |
|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|---------|---------|---------|---------|---------|
| AOM    | 0.003  | 0.006  | 0.013  | 0.016  | 0.018  | 0.021  | 0.029  | 0.044  | 0.043  | 0.048   | 0.054   | 0.077   | 0.117   | 0.181   | 0.330   |
| ARI    | 0.006  | 0.010  | 0.015  | 0.021  | 0.025  | 0.028  | 0.035  | 0.045  | 0.057  | 0.057   | 0.063   | 0.084   | 0.117   | 0.174   | 0.265   |
| ARI+LAM| 0.094  | 0.143  | 0.155  | 0.123  | 0.084  | 0.066  | 0.065  | 0.060  | 0.051  | 0.036   | 0.032   | 0.032   | 0.029   | 0.021   | 0.010   |
| ASE    | 0.444  | 0.205  | 0.158  | 0.082  | 0.039  | 0.021  | 0.015  | 0.008  | 0.007  | 0.006   | 0.005   | 0.004   | 0.002   | 0.003   | 0.001   |
| CAR    | 0.001  | 0.005  | 0.007  | 0.011  | 0.018  | 0.021  | 0.031  | 0.051  | 0.058  | 0.075   | 0.097   | 0.143   | 0.186   | 0.190   | 0.108   |
| LAM    | 0.231  | 0.295  | 0.200  | 0.105  | 0.063  | 0.040  | 0.025  | 0.017  | 0.009  | 0.006   | 0.006   | 0.002   | 0.001   | 0.001   | 0.000   |
| LIT    | 0.000  | 0.000  | 0.000  | 0.002  | 0.003  | 0.013  | 0.033  | 0.078  | 0.161  | 0.243   | 0.244   | 0.157   | 0.053   | 0.011   | 0.002   |
| LIT+OXC| 0.024  | 0.034  | 0.034  | 0.041  | 0.043  | 0.050  | 0.055  | 0.064  | 0.066  | 0.061   | 0.067   | 0.093   | 0.110   | 0.130   | 0.128   |
| LIT+VAL| 0.003  | 0.007  | 0.012  | 0.014  | 0.021  | 0.029  | 0.034  | 0.053  | 0.065  | 0.077   | 0.107   | 0.136   | 0.170   | 0.166   | 0.107   |
| OLA    | 0.000  | 0.001  | 0.003  | 0.007  | 0.011  | 0.026  | 0.060  | 0.110  | 0.165  | 0.177   | 0.150   | 0.126   | 0.099   | 0.049   | 0.017   |
| PAL    | 0.073  | 0.093  | 0.098  | 0.114  | 0.097  | 0.082  | 0.083  | 0.070  | 0.058  | 0.048   | 0.049   | 0.046   | 0.040   | 0.032   | 0.017   |
| QUE    | 0.008  | 0.028  | 0.059  | 0.105  | 0.147  | 0.166  | 0.161  | 0.133  | 0.080  | 0.048   | 0.029   | 0.019   | 0.011   | 0.006   | 0.001   |
| RISLAI | 0.018  | 0.041  | 0.059  | 0.081  | 0.089  | 0.085  | 0.099  | 0.110  | 0.098  | 0.079   | 0.072   | 0.065   | 0.056   | 0.035   | 0.014   |
| VAL    | 0.096  | 0.125  | 0.143  | 0.160  | 0.116  | 0.091  | 0.083  | 0.064  | 0.048  | 0.028   | 0.021   | 0.014   | 0.008   | 0.003   | 0.001   |
| PLA    | 0.001  | 0.007  | 0.045  | 0.120  | 0.227  | 0.260  | 0.193  | 0.095  | 0.034  | 0.012   | 0.005   | 0.002   | 0.000   | 0.000   | 0.000   |
| Drug  | SUCRA |
|-------|-------|
| ASE   | 0.91  |
| LAM   | 0.83  |
| PLA   | 0.73  |
| ARI+LAM | 0.68 |
| VAL   | 0.65  |
| QUE   | 0.64  |
| PAL   | 0.63  |
| RISLAI| 0.45  |
| LIT   | 0.37  |
| CAR   | 0.34  |
| OLA   | 0.33  |
| LIT+OXC| 0.27 |
| LIT+VAL| 0.27 |
| ARI   | 0.20  |
| AOM   | 0.18  |

**Comparison-adjusted funnel plot of studies of drugs versus placebo**
| Comparison     | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|---------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| AOM:PLA       | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| ARI:PLA       | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| ARI+LAM:LAM   | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| ASE:PLA       | 1                 | No concerns       | Suspected      | No concerns  | No concerns  | No concerns | No concerns | Moderate         |
| CAR:LIT       | 2                 | Major concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| LAM:LIT       | 1                 | Some concerns     | Suspected      | No concerns  | No concerns  | No concerns | No concerns | Low              |
| LAM:PLA       | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low         |
| LIT:LIT+OXC   | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| LIT:LIT+VAL   | 1                 | Major concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low         |
| LIT:OLA       | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| LIT:PLA       | 5                 | Some concerns     | Suspected      | No concerns  | No concerns  | No concerns | No concerns | Low              |
| LIT:QUE       | 1                 | Some concerns     | Suspected      | No concerns  | No concerns  | Major concerns | No concerns | Very low         |
| LIT:VAL       | 2                 | Major concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low         |
| LIT:VAL+VAL   | 1                 | Major concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low         |
| OLA:PLA       | 2                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| OLA:RISLAI    | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| PAL:PLA       | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| PLA:QUE       | 2                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| PLA:RISLAI    | 2                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:ARI       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:ARI+LAM   | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:ASE       | 0                 | No concerns       | Suspected      | No concerns  | No concerns  | No concerns | No concerns | Moderate         |
| AOM:CAR       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:LAM       | 0                 | Some concerns     | Suspected      | No concerns  | No concerns  | Major concerns | No concerns | Very low         |
| AOM:LIT       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:LIT+OXC   | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:LIT+VAL   | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:OLA       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:PAL       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:QUE       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:RISLAI    | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| AOM:VAL       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low              |
| Combination          | Concerns | Suspected | Major Concerns | No Concerns | Other Concerns | Level |
|----------------------|----------|-----------|----------------|-------------|---------------|-------|
| ARI:ARI+LAM          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:ASE              | 0        | No concerns | No concerns | No concerns | No concerns | Moderate |
| ARI:CAR              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:LAM              | 0        | Some concerns | No concerns | No concerns | Major concerns | No concerns | Very low |
| ARI:LIT              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:LIT+OXC          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:LIT+VAL          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:OLA              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:PAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:QUE              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:RISLAI           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:VAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:ASE          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:CAR          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:LAM          | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+LAM:LIT+OXC      | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:LIT+VAL      | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+LAM:OLA          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:PAL          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:QUE          | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+LAM:RISLAI       | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:VAL          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:CAR              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Moderate |
| ASE:LAM              | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low |
| ASE:LIT              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Moderate |
| ASE:LIT+OXC          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Moderate |
| ASE:LIT+VAL          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Moderate |
| ASE:OLA              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Moderate |
| ASE:PAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:QUE              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Moderate |
| ASE:RISLAI           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:VAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low   |
| Combination | Concerns Level | Suspected Level | No Concerns Level | Major Concerns Level | No Concerns Level | Very Low Level |
|-------------|----------------|-----------------|-------------------|----------------------|-------------------|----------------|
| CAR:LAM     | 0               | Some concerns   | No concerns        | No concerns           | Major concerns    | No concerns     | Very low       |
| CAR:LIT+OXC | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| CAR:LIT+VAL | 0               | Major concerns  | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| CAR:OLA     | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| CAR:PAL     | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| CAR:QUE     | 0               | Some concerns   | Suspected          | No concerns           | No concerns       | No concerns     | Very low       |
| CAR:RISLAI  | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| CAR:VAL     | 0               | Major concerns  | Suspected          | No concerns           | No concerns       | No concerns     | Very low       |
| LAM:LIT+OXC | 0               | Some concerns   | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| LAM:LIT+VAL | 0               | Some concerns   | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LAM:OLA     | 0               | Some concerns   | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| LAM:PAL     | 0               | Some concerns   | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| LAM:QUE     | 0               | Some concerns   | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| LAM:RISLAI  | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| LAM:VAL     | 0               | Some concerns   | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| LIT:PAL     | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LIT+OXC:LIT+VAL | 0       | Major concerns  | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| LIT+OXC:OLA | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LIT+OXC:PAL | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LIT+OXC:PLA | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LIT+OXC:QUE | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LIT+OXC:RISLAI | 0     | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LIT+OXC:VAL | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LIT+VAL:OLA | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LIT+VAL:PA L | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| LIT+VAL:PLA | 0               | Major concerns  | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| LIT+VAL:QUE | 0               | Major concerns  | Suspected          | No concerns           | Major concerns    | No concerns     | Very low       |
| LIT+VAL:RISLAI | 0     | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| OLA:PAL     | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| OLA:QUE     | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| OLA:VAL     | 0               | No concerns     | Suspected          | No concerns           | Major concerns    | No concerns     | Low            |
| Pair       | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low        |
|------------|---|-------------|-----------|-------------|----------------|-------------|-------------|------------|
| PAL:QUE    |   | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low        |
| PAL:RISLAI |   | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low        |
| PAL:VAL    |   | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low        |
| PLA:VAL    |   | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low   |
| QUE:RISLAI |   | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low        |
| QUE:VAL    |   | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low   |
| RISLAI:VAL |   | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low        |
## Meta-regression analysis

|                         | Primary analysis | Publication year | Duration of study | Number of total patients | Percent female | Mean age |
|-------------------------|------------------|------------------|-------------------|--------------------------|----------------|----------|
| Heterogeneity SD        | 0.184            | 0.506            | 0.548             | 0.556                    | 0.499          | 0.555    |
| Relative change in the variance | +175%         | +198%            | +202%             | +171%                    | +202%          |
| $\beta$, median (95% CI) | -0.030 (-1.566, 1.529) | -0.173 (-2.044, 1.581) | 0.030 (-0.858, 1.016) | 0.744 (-0.758, 2.345) | 0.084 (-1.140, 1.584) |

| Interventions vs placebo | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) |
|--------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| AOM                      | 7.000 (0.847, 57.876) | 4.120 (0.452, 50.658) | 3.883 (0.430, 45.114) | 4.110 (0.498, 44.598) | 3.352 (0.474, 40.674) | 3.858 (0.515, 44.710) |
| ARI                      | 6.385 (0.762, 53.464) | 3.685 (0.485, 44.975) | 3.901 (0.428, 47.418) | 3.739 (0.456, 42.449) | 2.075 (0.171, 29.699) | 3.674 (0.479, 51.096) |
| ARI+LAM                  | 0.858 (0.208, 3.541) | 0.740 (0.081, 6.542) | 0.707 (0.064, 6.567) | 0.743 (0.067, 6.586) | 0.774 (0.091, 5.992) | 0.772 (0.070, 6.854) |
| ASE                      | **0.363 (0.162, 0.812)** | 0.347 (0.055, 2.099) | 0.301 (0.036, 2.529) | 0.346 (0.066, 1.819) | 0.339 (0.069, 1.520) | 0.333 (0.055, 1.667) |
| CAR                      | 2.773 (0.894, 8.609) | 3.087 (0.646, 13.799) | 3.036 (0.579, 13.892) | 2.969 (0.573, 14.172) | 3.324 (0.723, 15.034) | 2.984 (0.597, 14.002) |
| LAM                      | 0.552 (0.177, 1.725) | 0.446 (0.091, 1.801) | 0.423 (0.073, 1.906) | 0.444 (0.084, 1.907) | 0.474 (0.098, 1.800) | 0.460 (0.091, 2.000) |
| LIT                      | **2.238 (1.430, 3.502)** | 2.108 (0.955, 4.386) | 2.076 (0.932, 4.285) | 2.071 (0.848, 4.675) | **2.268 (1.080, 4.855)** | 2.083 (0.923, 4.334) |
| LIT+OXC                  | 3.744 (0.617, 22.721) | 2.470 (0.232, 21.170) | 2.344 (0.231, 21.321) | 2.436 (0.226, 26.768) | 2.666 (0.256, 25.361) | 2.489 (0.249, 24.247) |
| LIT+VAL                  | **3.651 (1.234, 10.801)** | 3.003 (0.459, 16.411) | 2.846 (0.411, 16.240) | 2.829 (0.385, 15.099) | 3.116 (0.565, 16.187) | 2.886 (0.426, 16.273) |
| OLA                      | 1.814 (0.979, 3.361) | 2.082 (0.809, 6.541) | 2.050 (0.758, 6.761) | 2.091 (0.785, 6.920) | 2.120 (0.857, 6.788) | 2.134 (0.813, 7.562) |
| PAL                      | 1.217 (0.317, 4.668) | 0.994 (0.153, 6.493) | 1.207 (0.061, 29.006) | 0.985 (0.140, 6.460) | 1.033 (0.175, 6.956) | 0.997 (0.141, 7.003) |
| QUE                      | 1.162 (0.696, 1.937) | 1.121 (0.363, 3.220) | 1.072 (0.371, 3.282) | 1.071 (0.286, 4.044) | 1.032 (0.378, 2.934) | 1.101 (0.378, 3.249) |
| RISLAI                   | 1.788 (0.571, 5.605) | 1.366 (0.274, 5.706) | 1.407 (0.295, 6.430) | 1.360 (0.276, 6.290) | 1.587 (0.344, 6.969) | 1.447 (0.285, 7.244) |
| VAL                      | 1.117 (0.340, 3.666) | 0.784 (0.130, 3.395) | 0.747 (0.119, 3.384) | 0.758 (0.112, 3.472) | 0.838 (0.157, 3.740) | 0.748 (0.117, 3.520) |
| Sensitivity analysis | Primary analysis | Focusing on studies including only BDI | Focusing on studies including only non rapid-cycling BD patients | Focusing on double-blind studies | Focusing on non-enriched studies | Focusing on non-industry sponsorship studies |
|----------------------|------------------|--------------------------------------|---------------------------------------------------------------|--------------------------------|---------------------------------|-----------------------------------------------|
| Heterogeneity SD     | 0.184            | 0.452                                | 0.252                                                        | 0.405                          | 0.310                           | 0.277                                         |
| Relative change in the variance | +146%            | +37%                                 | +120%                                                       | +68%                           | +51%                            |                                               |
| Interventions vs placebo | RR (95% CrI)    | RR (95% CrI)                         | RR (95% CrI)                                                | RR (95% CrI)                   | RR (95% CrI)                    | RR (95% CrI)                                  |
| AOM                  | 7.000 (0.847, 57.876) | 3.955 (0.606, 55.263)               | 4.250 (0.713, 40.193)                                        | 3.900 (0.608, 40.169)          | 2.667 (0.318, 36.492)           | 2.835 (0.315, 33.341)                          |
| ARI                  | 6.385 (0.762, 53.464) | 3.673 (0.501, 40.399)               | 2.413 (0.303, 35.971)                                        | 3.683 (0.579, 37.341)          | 2.497 (0.263, 34.758)           | 2.693 (0.301, 44.934)                          |
| ARI+LAM              | 0.858 (0.208, 3.541) | 0.744 (0.080, 6.453)                | 0.633 (0.061, 5.713)                                         | 0.793 (0.099, 4.953)           | 0.640 (0.051, 5.794)            | 0.609 (0.052, 5.582)                           |
| ASE                  | **0.363 (0.162, 0.812)** | **0.333 (0.077, 1.420)**           | **0.344 (0.110, 1.039)**                                     | **0.335 (0.083, 1.294)**       | **0.311 (0.065, 1.288)**        | **0.315 (0.071, 1.230)**                        |
| CAR                  | 2.773 (0.894, 8.609) | 3.707 (0.628, 21.141)               | 3.370 (0.691, 19.373)                                        | 2.642 (0.599, 12.339)          | 2.760 (0.615, 10.153)           | 3.556 (0.898, 14.122)                          |
| LAM                  | 0.552 (0.177, 1.725) | 0.453 (0.086, 1.777)                | 0.362 (0.050, 1.795)                                         | 0.474 (0.109, 1.674)           | 0.368 (0.047, 1.754)            | 0.334 (0.045, 1.774)                           |
| LIT                  | **2.238 (1.430, 3.502)** | **2.083 (0.951, 4.175)**           | **1.829 (0.929, 3.455)**                                     | **2.126 (1.067, 3.965)**       | **1.786 (0.868, 3.417)**        | **1.795 (0.895, 3.495)**                        |
| LIT+OXC              | 3.744 (0.617, 22.721) | 1.751 (0.074, 23.917)               | 1.582 (0.108, 18.769)                                        | 2.457 (0.281, 20.116)          | 2.110 (0.262, 14.927)           | 2.101 (0.264, 16.898)                          |
| LIT+VAL              | **3.651 (1.234, 10.801)** | **2.993 (0.495, 14.693)**          | **2.268 (0.445, 11.617)**                                    | **2.555 (0.424, 14.690)**      | **2.484 (0.544, 9.529)**        | **2.474 (0.595, 10.119)**                       |
| OLA                  | 1.814 (0.979, 3.361) | 2.015 (0.854, 6.360)                | 1.575 (0.722, 3.824)                                         | 1.982 (0.914, 5.638)           | 1.498 (0.654, 4.066)            | 1.526 (0.665, 4.061)                           |
| PAL                  | 1.217 (0.317, 4.668) | 0.996 (0.180, 6.406)                | 0.996 (0.212, 4.607)                                         | 0.995 (0.175, 5.646)           | 0.782 (0.081, 6.006)            | 0.815 (0.103, 5.996)                           |
| QUE                  | 1.162 (0.696, 1.937) | 1.117 (0.405, 2.923)                | 1.001 (0.421, 2.267)                                         | 1.093 (0.447, 2.646)           | 1.004 (0.401, 2.389)            | 0.991 (0.414, 2.397)                           |
| RISLAI               | 1.788 (0.571, 5.605) | 1.369 (0.325, 5.472)                | 1.267 (0.350, 4.196)                                         | 1.350 (0.343, 5.150)           | 0.942 (0.143, 4.692)            | 0.991 (0.163, 4.574)                           |
| VAL                  | 1.117 (0.340, 3.666) | 0.816 (0.130, 3.628)                | 0.561 (0.073, 2.696)                                         | 0.635 (0.096, 3.063)           | 0.679 (0.134, 2.361)            | 0.655 (0.153, 2.573)                           |
1.6. Mortality rate (11 RCTs, 4703 patients)
League table (odds ratio)

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.
The boldface result indicates statistical significance.

|               | AOM     | ARI+LAM | ASE     | LAM     | LIT     | LIT+VAL | OLA     | PAL     | QUE     | RISLAI  | VAL     |
|---------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|               | 1.950   | 1.550   | 0.627   | 2.138   | 0.491   | 0.201   | 1.110   | 0.660   | 1.008   | 1.636   | 0.855   |
|               | (0.006, 0.003, 747.026) | (0.0219, 49.259) | (0.005, 74.010) | (0.086, 42.921) | (0.088, 2.736) | (0.010, 4.210) | (0.022, 56.070) | (0.108, 611.674) | (0.020, 51.157) | (0.003, 223.699) | (0.063, 11.698) |
|               | 3.022   | 3.022   | 1.784   | 1.396   | 0.491   | 0.201   | 1.110   | 0.660   | 1.008   | 1.636   | 0.855   |
|               | (0.028, 1.550) | (0.023, 325.642) | (0.008, 139.379) | (0.056, 34.488) | (0.024, 2.736) | (0.010, 4.210) | (0.022, 56.070) | (0.108, 611.674) | (0.020, 51.157) | (0.003, 223.699) | (0.063, 11.698) |
|               | 5.391   | 2.765   | 0.875   | 0.833   | 0.293   | 0.233   | 1.310   | 0.366   | 0.408   | 1.148   | 1.008   |
|               | (0.130, 1.550) | (0.009, 1.56.132) | (0.008, 94.812) | (0.025, 27.699) | (0.024, 3.593) | (0.004, 12.414) | (0.057, 30.250) | (0.003, 8.896) | (0.009, 18.673) | (0.014, 95.890) | (0.020, 51.157) |
|               | 2.645   | 1.357   | 0.522   | 0.326   | 0.115   | 0.223   | 0.823   | 0.643   | 0.404   | 0.643   | 0.660   |
|               | (0.044, 1.550) | (0.004, 90.731) | (0.004, 60.637) | (0.006, 19.163) | (0.003, 8.896) | (0.019, 12.414) | (0.029, 54.949) | (0.004, 8.896) | (0.009, 18.673) | (0.014, 95.890) | (0.018, 56.070) |
|               | 1.578   | 0.809   | 0.204   | 0.182   | 0.643   | 0.219   | 2.265   | 0.628   | 1.028   | 1.310   | 1.636   |
|               | (0.024, 1.550) | (0.004, 314.536) | (0.001, 29.412) | (0.063, 53.367) | (0.004, 8.896) | (0.079, 49.665) | (0.102, 132.013) | (0.009, 42.085) | (0.042, 24.961) | (0.003, 54.136) | (0.024, 113.488) |
|               | 3.465   | 1.777   | 1.147   | 1.148   | 0.404   | 1.319   | 2.265   | 0.628   | 1.028   | 1.310   | 1.636   |
|               | (0.071, 3.465) | (0.010, 314.536) | (0.013, 102.545) | (0.014, 95.890) | (0.009, 18.673) | (0.036, 53.367) | (0.102, 132.013) | (0.009, 42.085) | (0.042, 24.961) | (0.014, 95.890) | (0.024, 113.488) |
|               | 2.176   | 1.116   | 0.720   | 1.148   | 0.404   | 0.823   | 1.346   | 0.628   | 1.028   | 1.310   | 1.636   |
|               | (0.017, 2.176) | (0.004, 413.642) | (0.003, 154.054) | (0.014, 95.890) | (0.009, 18.673) | (0.012, 54.949) | (0.294, 6.159) | (0.009, 42.085) | (0.042, 24.961) | (0.014, 95.890) | (0.024, 113.488) |
|               | 3.560   | 1.826   | 1.178   | 1.148   | 0.404   | 1.319   | 2.265   | 0.628   | 1.028   | 1.310   | 1.636   |
|               | (0.057, 3.560) | (0.011, 299.645) | (0.011, 132.013) | (0.014, 95.890) | (0.009, 18.673) | (0.036, 53.367) | (0.102, 132.013) | (0.009, 42.085) | (0.042, 24.961) | (0.014, 95.890) | (0.024, 113.488) |
|               | 3.046   | 1.156   | 1.008   | 1.148   | 0.404   | 0.823   | 1.346   | 0.628   | 1.028   | 1.310   | 1.636   |
|               | (0.123, 3.046) | (0.013, 183.975) | (0.020, 51.188) | (0.014, 95.890) | (0.009, 18.673) | (0.012, 54.949) | (0.294, 6.159) | (0.009, 42.085) | (0.042, 24.961) | (0.014, 95.890) | (0.024, 113.488) |

Odds ratio (95% CI)
### Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|---------------------------------------------------|
| 0.01                             | Low                      | Q        | df | p       |
|                                  |                          | 0.472   | 4  | 0.976   |

### Inconsistency

|                  | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures |
|------------------|-----------------|--------------------|----------------------|------------------------|
|                  |                 |                    |                      | Ratio of risk ratios   | P value               |
| LAM vs LIT       | 2.844 (0.190, 42.657) | 2.138 (0.086, 52.921) | 5.762 (0.037, 895.874) | 0.371 (0.001, 146.775) | 0.745                |
| LAM vs PLA       | 2.138 (0.086, 52.921) | 1.607 (0.107, 24.100) | 0.793 (0.005, 123.322) | 2.695 (0.007, 1066.353) | 0.756                |
| LIT vs OLA       | 0.293 (0.024, 3.593) | 0.201 (0.010, 4.210) | 0.650 (0.008, 54.348) | 0.309 (0.001, 66.533) | 0.668                |
| LIT vs QUE       | 0.643 (0.046, 8.896) | 1.110 (0.022, 56.070) | 0.412 (0.012, 14.188) | 2.693 (0.014, 530.330) | 0.713                |
| LIT vs PLA       | 0.565 (0.085, 3.736) | 0.650 (0.080, 5.306) | 0.313 (0.004, 23.587) | 2.077 (0.017, 253.966) | 0.766                |
| OLA vs RISLAI    | 1.379 (0.036, 53.346) | 1.008 (0.020, 51.157) | 10.534 (0.000, 231723.470) | 0.096 (0.000, 4426.215) | 0.668                |
| OLA vs PLA       | 1.930 (0.132, 28.121) | 1.030 (0.020, 52.311) | 3.332 (0.085, 130.035) | 0.309 (0.001, 66.533) | 0.668                |
| QUE vs PLA       | 0.879 (0.099, 7.797) | 1.007 (0.104, 9.709) | 0.154 (0.000, 516.306) | 6.555 (0.001, 30055.471) | 0.662                |
| RISLAI vs PLA    | 1.399 (0.036, 54.136) | 1.023 (0.020, 51.915) | 10.693 (0.000, 235390.237) | 0.096 (0.000, 4428.428) | 0.668                |
|        | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 | Rank 11 | Rank 12 |
|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|---------|---------|
| AOM    | 0.000  | 0.001  | 0.002  | 0.002  | 0.009  | 0.014  | 0.048  | 0.097  | 0.193  | 0.197   | 0.246   | 0.191   |
| ARI+LAM| 0.044  | 0.028  | 0.012  | 0.031  | 0.048  | 0.037  | 0.022  | 0.034  | 0.054  | 0.081   | 0.156   | 0.454   |
| ASE    | 0.231  | 0.078  | 0.016  | 0.098  | 0.128  | 0.103  | 0.058  | 0.075  | 0.061  | 0.077   | 0.055   | 0.020   |
| LAM    | 0.000  | 0.000  | 0.001  | 0.003  | 0.013  | 0.026  | 0.045  | 0.116  | 0.244  | 0.253   | 0.216   | 0.083   |
| LIT    | 0.259  | 0.326  | 0.250  | 0.115  | 0.036  | 0.011  | 0.003  | 0.001  | 0.000  | 0.000   | 0.000   | 0.000   |
| LIT+VAL| 0.082  | 0.195  | 0.339  | 0.227  | 0.100  | 0.038  | 0.013  | 0.006  | 0.001  | 0.001   | 0.000   | 0.000   |
| OLA    | 0.005  | 0.011  | 0.019  | 0.196  | 0.204  | 0.122  | 0.076  | 0.099  | 0.103  | 0.077   | 0.050   | 0.038   |
| PAL    | 0.000  | 0.000  | 0.001  | 0.002  | 0.004  | 0.016  | 0.049  | 0.113  | 0.193  | 0.235   | 0.221   | 0.167   |
| QUE    | 0.004  | 0.019  | 0.014  | 0.036  | 0.132  | 0.244  | 0.280  | 0.193  | 0.067  | 0.011   | 0.001   | 0.000   |
| RISLAI | 0.238  | 0.073  | 0.023  | 0.083  | 0.138  | 0.106  | 0.053  | 0.069  | 0.053  | 0.064   | 0.054   | 0.047   |
| VAL    | 0.138  | 0.266  | 0.312  | 0.176  | 0.067  | 0.025  | 0.011  | 0.004  | 0.001  | 0.000   | 0.000   | 0.000   |
| PLA    | 0.001  | 0.004  | 0.013  | 0.032  | 0.123  | 0.258  | 0.344  | 0.192  | 0.031  | 0.003   | 0.001   | 0.000   |
SUCRA

| Drug  | SUCRA |
|-------|-------|
| LIT   | 0.87  |
| VAL   | 0.82  |
| LIT+VAL | 0.78 |
| RISLAI| 0.66  |
| QUE   | 0.60  |
| PLA   | 0.59  |
| ASE   | 0.43  |
| OLA   | 0.37  |
| AOM   | 0.23  |
| LAM   | 0.23  |
| PAL   | 0.23  |
| ARI+LAM | 0.19 |
| Comparison     | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|----------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|-------------------|
| AOM:PLA        | 1                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+LAM:LAM    | 1                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ASE:PLA        | 1                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LAM:LIT        | 1                 | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LAM:PLA        | 1                 | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:LIT+VAL    | 1                 | Major concerns   | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:OLA        | 1                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:PLA        | 3                 | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:QUE        | 1                 | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:VAL        | 1                 | Major concerns   | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT+VAL:VAL    | 1                 | Major concerns   | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| OLA:PLA        | 1                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| OLA:RISLAI     | 1                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PAL:PLA        | 1                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PLA:QUE        | 2                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PLA:RISLAI     | 1                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:ARI+LAM    | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:ASE        | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:LAM        | 0                 | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| AOM:LIT        | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:LIT+VAL    | 0                 | Major concerns   | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| AOM:OLA        | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:PAL        | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:QUE        | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:RISLAI     | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:VAL        | 0                 | Major concerns   | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| ARI+LAM:ASE    | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+LAM:LIT    | 0                 | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| ARI+LAM:LIT+VAL| 0                 | Major concerns   | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| ARI+LAM:OLA    | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+LAM:PAL    | 0                 | No concerns      | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+LAM:PLA    | 0                 | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| Combination          | Score | Concerns Status | Concerns Status | Concerns Status | Concerns Status | Concerns Status | Concerns Status | Concerns Status | Strategy |
|----------------------|-------|-----------------|-----------------|-----------------|-----------------|-----------------|----------------|----------------|----------|
| ARI+LAM:QUE          | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| ARI+LAM:RISLAI       | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| ARI+LAM:VAL          | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| ASE:LAM              | 0     | Some concerns   | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| ASE:LIT              | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| ASE:LIT+VAL          | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| ASE:OLA              | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| ASE:PAL              | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| ASE:QUE              | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| ASE:RISLAI           | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| ASE:VAL              | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| LAM:LIT+VAL          | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| LAM:OLA              | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| LAM:PAL              | 0     | Some concerns   | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| LAM:QUE              | 0     | Some concerns   | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| LAM:RISLAI           | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| LAM:VAL              | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| LIT:PAL              | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| LIT:RISLAI           | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| LIT+VAL:OLA          | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| LIT+VAL:PAL          | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| LIT+VAL:PLA          | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| LIT+VAL:QUE          | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| LIT+VAL:RISLAI       | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| OLA:PAL              | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| OLA:QUE              | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| PAL:QUE              | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| PAL:RISLAI           | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| PAL:VAL              | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| PLA:VAL              | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| QUE:RISLAI           | 0     | No concerns     | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Low            |          |
| QUE:VAL              | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
| RISLAI:VAL           | 0     | Major concerns  | Suspected       | No concerns     | Major concerns  | No concerns     | No concerns     | Very low        |          |
### Raw data for mortality rate

| Intervention  | n  | Total patients | Intervention  | n  | Total patients | Intervention  | n  | Total patients |
|---------------|----|----------------|---------------|----|----------------|---------------|----|----------------|
| Amsterdam 2010 | LIT |               |               | PLA |               |               | PLA |               |
| Berwaerts 2012 | PAL | 2              | PLA           | 0  | 148           |
| Bowden 2000    | DIV |                | LIT           | PLA |               |               | PLA |               |
| Bowden 2003    | LAM |                | LIT           | PLA |               |               | PLA |               |
| Bowden 2012    | LAM+VAL |           | LAM           |     |               |               | PLA |               |
| Calabrese 2000 | LAM |                | PLA           |     |               |               | PLA |               |
| Calabrese 2003 | LAM | 1              | LIT           | 0  | 121           | PLA           | 0  | 121           |
| Calabrese 2005 | DIV |                | LIT           |     |               |               | PLA |               |
| Calabrese 2017 | AOM | 1              | PLA           | 0  | 133           |
| Carlson 2012   | ARI+LAM | 0            | LAM           | 0  | 173           |
| Coxhead 1992   | CAR |                | LIT           |     |               |               | PLA |               |
| Cundall 1972   | LIT |                | PLA           |     |               |               | PLA |               |
| Dunner 1976    | LIT |                | PLA           |     |               |               | PLA |               |
| Fieve 1976     | LIT |                | PLA           |     |               |               | PLA |               |
| Geddes 2010    | LIT | 2              | VAL           | 3  | 110           | LIT+VAL       | 4  | 110           |
| Hartong 2003   | CAR |                | LIT           |     |               |               | PLA |               |
| Kane 1982      | LIT |                | PLA           |     |               |               | PLA |               |
| Keck 2007      | ARI |                | PLA           |     |               |               | PLA |               |
| Kleindienst 2000 | CAR |               | LIT           |     |               |               | PLA |               |
| Koyama 2011    | LAM |                | PLA           |     |               |               | PLA |               |
| Melia 1970     | LIT |                | PLA           |     |               |               | PLA |               |
| Prien 1973a    | LIT |                | PLA           |     |               |               | PLA |               |
| Prien 1973b    | LIT | 0              | PLA           | 1  | 104           |
| Quiroz 2010    | RIS-LAI |              | PLA           |     |               |               | PLA |               |
| Study          | Intervention | n | Total patients | Intervention | n | Total patients |
|---------------|--------------|---|----------------|--------------|---|----------------|
| Szegedi 2018  | ASE          | 0 | 126            | PLA          | 0 | 127            |
| Tohen 2005    | LIT          | 0 | 214            | OLA          | 2 | 217            |
| Tohen 2006    | OLA          |   |                | PLA          |   |                |
| Vieta 2008    | LIT+OXC      |   |                | LIT          |   |                |
| Vieta 2012    | OLA          | 0 | 131            | RISLAI       | 0 | 132            | PLA | 0 | 135              |
| Weisler 2011  | LIT          | 0 | 364            | QUE          | 0 | 404            | PLA | 0 | 404              |
| Woo 2011      | ARI+VAL      |   |                | VAL          |   |                |
| Young 2014    | QUE          | 1 | 291            | PLA          | 1 | 294            |
1.7. Completed suicide (25 RCTs, 6742 patients)

League table (odds ratio)

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

| AOM        | 0.947 (0.004, 245.452) | 1.235 (0.004, 430.523) | 1.000 (0.007, 258.243) | 0.709 (0.016, 92.333) | 1.200 (0.024, 362.745) | 1.479 (0.010, 74.604) | 0.861 (0.002, 54.615) | 0.343 (0.010, 127.485) | 0.974 (0.009, 110.686) | 1.153 (0.009, 171.075) | 0.974 (0.009, 110.686) | 1.008 (0.020, 51.152) |
| ARI        | 1.304 (0.004, 455.958) | 1.055 (0.004, 273.554) | 0.749 (0.007, 75.452) | 1.267 (0.025, 97.899) | 1.697 (0.010, 284.291) | 0.909 (0.002, 79.091) | 0.362 (0.002, 57.870) | 1.218 (0.011, 135.125) | 1.028 (0.009, 117.308) | 1.843 (0.019, 181.345) | 1.064 (0.021, 54.261) | 
| ARI+LAM    | 0.809 (0.002, 282.280) | 0.574 (0.004, 75.573) | 0.972 (0.019, 98.978) | 1.198 (0.015, 373.307) | 1.301 (0.005, 61.320) | 0.697 (0.006, 84.184) | 0.934 (0.005, 143.079) | 0.789 (0.005, 125.776) | 1.414 (0.011, 185.082) | 0.816 (0.011, 62.659) | 
| ASE        | 0.710 (0.007, 71.229) | 1.201 (0.016, 92.398) | 1.480 (0.024, 90.486) | 1.608 (0.007, 362.963) | 0.861 (0.010, 74.657) | 0.343 (0.002, 54.647) | 1.154 (0.010, 127.574) | 0.975 (0.009, 110.753) | 1.746 (0.018, 171.177) | 1.008 (0.020, 51.188) | 
| CAR        | 1.692 (0.009, 30.695) | 2.085 (0.021, 16.683) | 2.266 (0.036, 141.189) | 2.124 (0.060, 24.670) | 0.483 (0.009, 26.736) | 1.626 (0.053, 49.576) | 1.373 (0.040, 46.726) | 2.461 (0.122, 49.665) | 1.420 (0.127, 15.836) | 1.000 (0.131, 5.358) | 
| 0.972 (0.019, 49.259) | 1.233 (0.016, 9.280) | 1.339 (0.023, 78.878) | 0.717 (0.046, 11.236) | 0.285 (0.007, 11.610) | 0.961 (0.041, 22.376) | 0.812 (0.033, 20.136) | 1.454 (0.081, 26.172) | 0.839 (0.131, 5.358) | 1.180 (0.135, 10.325) | 0.681 (0.201, 2.310) | 
| LAM        | 2.085 (0.021, 16.683) | 0.744 (0.046, 12.002) | 1.086 (0.031, 38.621) | 0.582 (0.066, 5.143) | 0.232 (0.007, 7.174) | 0.780 (0.052, 11.741) | 0.658 (0.038, 11.371) | 1.180 (0.135, 10.325) | 0.681 (0.201, 2.310) | 0.627 (0.015, 26.243) | 
| LIT        | 1.000 (0.020, 50.846) | 0.536 (0.008, 34.405) | 0.213 (0.002, 29.309) | 0.718 (0.008, 62.091) | 0.606 (0.006, 56.753) | 1.086 (0.031, 38.621) | 0.627 (0.015, 26.243) |
|          | OLA      |          |          |          |          |          |
|----------|----------|----------|----------|----------|----------|----------|
|          |          |          |          |          |          |          |
|          |          | 0.336    | (0.014, 8.305) | 0.398    | (0.009, 18.601) | 1.340    | (0.050, 36.107) | 1.132    | (0.057, 22.347) | 2.028    | (0.099, 41.421) | 1.170    | (0.141, 9.729) |
|          |          |          |          |          |          |          |
|          |          |          | PAL      |          | 3.366    | (0.054, 208.159) | 2.843    | (0.045, 181.417) | 5.095    | (0.095, 274.486) | 2.941    | (0.119, 72.762) |
|          |          | 1.110    | (0.022, 56.070) |          |          | QUE      | 0.845    | (0.021, 33.717) | 1.514    | (0.050, 45.847) | 0.874    | (0.065, 11.664) |
|          |          |          |          |          |          |          |          |          |          |          |          |          |
|          |          |          |          | 1.008    | (0.020, 51.157) | RISLAI   | 1.792    | (0.054, 59.704) | 1.034    | (0.074, 14.509) |          |          |          |
|          |          |          |          |          |          |          |          |          |          |          |          |          |
| 1.008    | (0.020, 51.152) | 1.064    | (0.021, 54.261) | 1.008    | (0.020, 51.188) | 1.008    | (0.141, 7.200) | 0.737    | (0.197, 2.764) | 0.790    | (0.049, 12.683) | 2.941    | (0.119, 72.762) | 1.005    | (0.063, 16.103) | 0.993    | (0.062, 15.959) | 0.504    | (0.010, 25.598) |
| PLAIN    | (0.125, 11.814) |          | (0.020, 50.846) | 1.000    |          |          |          |          |          |          |          |          |

**Evaluation of heterogeneity and inconsistency**

| Between study variance ($r^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model | Q | df | p   |
|-------------------------------|--------------------------|-----------------------------------------------------|----|----|-----|
| 0.01                          | Low                      |                                                     | 0.746 | 10 | 1.000 |
|                  | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures |
|------------------|-----------------|--------------------|----------------------|------------------------|
|                  | Ratio of risk ratios | P value |             |                        |
| LAM vs LIT       | 1.233 (0.164, 9.280) | 0.744 (0.046, 12.002) | 2.163 (0.115, 40.740) | 0.344 (0.006, 19.613) | 0.605 |
| LAM vs PLA       | 0.839 (0.131, 5.358) | 1.008 (0.141, 7.200) | 0.195 (0.001, 50.496) | 5.160 (0.014, 1870.386) | 0.585 |
| LIT vs LIT+VAL   | 1.086 (0.031, 38.621) | 1.000 (0.020, 50.846) | 1.610 (0.000, 8453.197) | 0.621 (0.000, 7694.030) | 0.921 |
| LIT vs OLA       | 0.582 (0.066, 5.143) | 0.336 (0.014, 8.305) | 0.931 (0.048, 18.169) | 0.361 (0.005, 28.580) | 0.648 |
| LIT vs QUE       | 0.780 (0.052, 11.741) | 1.110 (0.022, 56.070) | 0.564 (0.013, 24.085) | 1.967 (0.009, 448.631) | 0.807 |
| LIT vs VAL       | 1.180 (0.135, 10.325) | 1.217 (0.125, 11.814) | 0.856 (0.001, 1236.080) | 1.422 (0.001, 2902.420) | 0.928 |
| LIT vs PLA       | 0.681 (0.201, 2.310) | 0.737 (0.197, 2.764) | 0.428 (0.018, 10.463) | 1.722 (0.054, 54.735) | 0.758 |
| LIT+VAL vs VAL   | 1.086 (0.031, 38.621) | 1.000 (0.020, 50.846) | 1.610 (0.000, 8453.197) | 0.621 (0.000, 7694.030) | 0.921 |
| OLA vs RISLAI    | 1.132 (0.057, 22.347) | 1.008 (0.020, 51.157) | 1.326 (0.014, 130.061) | 0.760 (0.002, 318.493) | 0.929 |
| OLA vs PLA       | 1.170 (0.141, 9.729) | 0.790 (0.049, 12.683) | 2.023 (0.076, 53.512) | 0.390 (0.005, 28.586) | 0.668 |
| QUE vs PLA       | 0.874 (0.065, 11.664) | 1.005 (0.063, 16.103) | 0.333 (0.000, 479.191) | 3.017 (0.001, 7232.210) | 0.781 |
| RISLAI vs PLA    | 1.034 (0.074, 14.509) | 0.993 (0.062, 15.959) | 1.519 (0.000, 7872.256) | 0.654 (0.000, 5255.866) | 0.926 |
| VAL vs PLA       | 0.577 (0.054, 6.149) | 0.504 (0.010, 25.598) | 0.623 (0.032, 12.081) | 0.808 (0.006, 110.819) | 0.932 |
|       | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 | Rank 11 | Rank 12 | Rank 13 | Rank 14 |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| AOM   | 0.085  | 0.078  | 0.087  | 0.090  | 0.096  | 0.088  | 0.066  | 0.067  | 0.060  | 0.065  | 0.073  | 0.062  | 0.050  | 0.032  |
| ARI   | 0.101  | 0.098  | 0.078  | 0.080  | 0.074  | 0.073  | 0.073  | 0.065  | 0.061  | 0.053  | 0.062  | 0.061  | 0.065  | 0.057  |
| ARI+LAM | 0.095 | 0.115  | 0.080  | 0.068  | 0.065  | 0.062  | 0.062  | 0.046  | 0.045  | 0.038  | 0.046  | 0.060  | 0.079  | 0.141  |
| ASE   | 0.113  | 0.074  | 0.062  | 0.062  | 0.056  | 0.058  | 0.074  | 0.072  | 0.057  | 0.054  | 0.054  | 0.067  | 0.103  | 0.095  |
| CAR   | 0.000  | 0.005  | 0.013  | 0.020  | 0.025  | 0.038  | 0.046  | 0.061  | 0.087  | 0.105  | 0.120  | 0.129  | 0.151  | 0.200  |
| LAM   | 0.109  | 0.158  | 0.140  | 0.099  | 0.105  | 0.097  | 0.071  | 0.061  | 0.035  | 0.024  | 0.032  | 0.032  | 0.024  | 0.012  |
| LIT   | 0.021  | 0.060  | 0.104  | 0.140  | 0.178  | 0.192  | 0.134  | 0.105  | 0.053  | 0.012  | 0.001  | 0.000  | 0.000  | 0.000  |
| LIT+VAL | 0.172 | 0.133  | 0.123  | 0.125  | 0.088  | 0.070  | 0.057  | 0.046  | 0.039  | 0.035  | 0.032  | 0.033  | 0.035  | 0.013  |
| OLA   | 0.000  | 0.003  | 0.009  | 0.028  | 0.052  | 0.074  | 0.113  | 0.125  | 0.135  | 0.135  | 0.118  | 0.105  | 0.070  | 0.034  |
| PAL   | 0.000  | 0.000  | 0.000  | 0.000  | 0.000  | 0.001  | 0.004  | 0.009  | 0.022  | 0.053  | 0.108  | 0.183  | 0.255  | 0.365  |
| QUE   | 0.130  | 0.112  | 0.093  | 0.071  | 0.073  | 0.050  | 0.067  | 0.085  | 0.064  | 0.054  | 0.054  | 0.064  | 0.058  | 0.025  |
| RISLAI | 0.083  | 0.071  | 0.103  | 0.096  | 0.076  | 0.079  | 0.071  | 0.060  | 0.078  | 0.068  | 0.072  | 0.076  | 0.049  | 0.019  |
| VAL   | 0.091  | 0.095  | 0.107  | 0.122  | 0.110  | 0.103  | 0.130  | 0.090  | 0.051  | 0.035  | 0.028  | 0.022  | 0.012  | 0.006  |
| PLA   | 0.000  | 0.000  | 0.000  | 0.000  | 0.001  | 0.016  | 0.033  | 0.110  | 0.213  | 0.271  | 0.201  | 0.105  | 0.048  | 0.002  |
SUCRA

| Drug     | SUCRA |
|----------|-------|
| LIT+VAL  | 0.84  |
| VAL      | 0.83  |
| QUE      | 0.75  |
| RISLAI   | 0.74  |
| LIT      | 0.70  |
| PLA      | 0.55  |
| ARI      | 0.43  |
| AOM      | 0.40  |
| ASE      | 0.36  |
| OLA      | 0.36  |
| LAM      | 0.30  |
| CAR      | 0.30  |
| ARI+LAM  | 0.22  |
| PAL      | 0.22  |
| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|------------------|------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| AOM:PLA    | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| ARI:PLA    | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| ARI+LAM:LAM| 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| ASE:PLA    | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| CAR:LIT    | 3                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LAM:LIT    | 2                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LAM:PLA    | 4                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LIT:LIT+VAL| 1                | Major concerns   | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LIT:OLA    | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| LIT:PLA    | 8                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| LIT:QUE    | 1                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LIT:QUE    | 1                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| LI:QUE     | 3                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| LI+VAL:VAL | 1                | Major concerns   | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Very low         |
| PLA:PLA    | 2                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| PLA:QUE    | 2                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| PLA:RISLAI | 2                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| PL:VAL     | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:ARI    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:ARI+LAM| 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:ASE    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:CAR    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:LAM    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:LIT    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:LIT+VAL| 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:OLA    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:PAL    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:QUE    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:RISLAI | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| AOM:VAL    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| ARI:ARI+LAM| 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns    | No concerns  | Low              |
| Combination            | Concerns | Suspected | Major Concerns | No Concerns | No Concerns | Low       |
|------------------------|----------|----------|----------------|-------------|-------------|-----------|
| ARI:ASE                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI:CAR                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI:LAM                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI:LIT                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI:LIT+VAL            | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+OLI                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+PAC                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+QUE                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+RISLAI             | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+VAL                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:ASE            | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:CAS           | 0        | Some concerns | No concerns  | Major concerns | No concerns | No concerns | Very low |
| ARI+LAM:LIT            | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:LIT+VAL        | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:OLA            | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:PAL            | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:PLA            | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:QUE            | 0        | Some concerns | Suspected     | Major concerns | No concerns | No concerns | Very low   |
| ARI+LAM:RISLAI         | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ASE:CAR                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ASE:LAM                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ASE:LIT                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ASE:LIT+VAL            | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ASE:OLA                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ASE:PAL                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ASE:QUE                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ASE:RISLAI             | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| ASE:VAL                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| CAR:LAM                | 0        | Some concerns | No concerns  | Major concerns | No concerns | No concerns | Very low   |
| CAR:LIT+VAL            | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Very low   |
| CAR:OLA                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| CAR:PAL                | 0        | No concerns | No concerns  | Major concerns | No concerns | No concerns | Low       |
| Combination       | Score | Concerns            | Suspected | Major Concerns | No Concerns | Concerns | Very Low |
|-------------------|-------|---------------------|-----------|----------------|-------------|----------|----------|
| CAR:PLA           | 0     | Some concerns       | Suspected | No concerns    | Major concerns | No concerns | No concerns | Very low |
| CAR:QUE           | 0     | Some concerns       | Suspected | No concerns    | Major concerns | No concerns | No concerns | Very low |
| CAR:RISLAI        | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| CAR:VAL           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LAM:LIT+VAL       | 0     | Major concerns      | Suspected | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM:OLA           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LAM:PAL           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LAM:QUE           | 0     | Some concerns       | Suspected | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LAM:RISLAI        | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LAM:VAL           | 0     | Some concerns       | Suspected | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LIT:PAL           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT:RISLAI        | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT+VAL:OLA       | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT+VAL:PAL       | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| LIT+VAL:PLA       | 0     | Major concerns      | Suspected | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LIT+VAL:QUE       | 0     | Major concerns      | Suspected | No concerns    | Major concerns | No concerns | No concerns | Very low |
| LIT+VAL:RISLAI    | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| OLA:PAL           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| OLA:QUE           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| OLA:VAL           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| PAL:QUE           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| PAL:RISLAI        | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| PAL:VAL           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| QUE:RISLAI        | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| QUE:VAL           | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
| RISLAI:VAL        | 0     | No concerns         | Suspected | No concerns    | Major concerns | No concerns | No concerns | Low      |
## Raw data for completed suicide

| Intervention | n | Total patients | Intervention | n | Total patients | Intervention | n | Total patients |
|--------------|---|----------------|--------------|---|----------------|--------------|---|----------------|
| Amsterdam 2010 | LIT | 0 | 26 | PLA | 0 | 27 |
| Berwaerts 2012 | PAL | 1 | 152 | PLA | 0 | 148 |
| Bowden 2000 | DIV | 0 | 187 | LIT | 0 | 91 | PLA | 0 | 94 |
| Bowden 2003 | LAM | 0 | 59 | LIT | 0 | 46 | PLA | 0 | 70 |
| Bowden 2012 | LAM+VAL | LAM |
| Calabrese 2000 | LAM | 0 | 93 | PLA | 0 | 89 |
| Calabrese 2003 | LAM | 0 | 171 | LIT | 0 | 121 | PLA | 0 | 121 |
| Calabrese 2005 | DIV | 0 | 28 | LIT | 0 | 32 |
| Calabrese 2017 | AOM | 0 | 132 | PLA | 0 | 133 |
| Carlson 2012 | ARI+LAM | LAM |
| Coxhead 1992 | CAR | 2 | 15 | LIT | 0 | 16 |
| Cundall 1972 | LIT |
| Dunner 1976 | LIT |
| Fieve 1976 | LIT | PLA |
| Geddes 2010 | LIT | 0 | 110 | VAL | 0 | 110 | LIT+VAL | 0 | 110 |
| Hartong 2003 | CAR | 0 | 30 | LIT | 0 | 23 |
| Kane 1982 | LIT | 0 | 4 | PLA | 0 | 7 |
| Keck 2007 | ARI | 0 | 78 | PLA | 0 | 83 |
| Kleindienst 2000 | CAR | 0 | 85 | LIT | 0 | 86 |
| Koyama 2011 | LAM | 0 | 45 | PLA | 0 | 58 |
| Melia 1970 | LIT | PLA |
| Prien 1973a | LIT | 0 | 18 | PLA | 1 | 13 |
| Prien 1973b | LIT | 0 | 101 | PLA | 1 | 104 |
| Quiroz 2010 | RIS-LAI | 0 | 140 | PLA | 0 | 135 |
| Szegedi 2018 | ASE | 0 | 126 | PLA | 0 | 127 |
| Authors  | Intervention | n | Total patients | Authors  | Intervention | n | Total patients |
|---------|--------------|---|----------------|---------|--------------|---|----------------|
| Tohen 2005 | LIT          | 0 | 214            | OLA     | 1            | 217 |
| Tohen 2006 | OLA          | 0 | 225            | PLA     | 0            | 136 |
| Vieta 2008 | LIT+OXC      |   |                | LIT     |              |    |
| Vieta 2012 | OLA          | 0 | 131            | RISLAI  | 0            | 132 |
|          |              |   |                | PLA     | 0            | 135 |
| Weisler 2011 | LIT         | 0 | 364            | QUE     | 0            | 404 |
|          |              |   |                | PLA     | 0            | 404 |
| Woo 2011 | ARI+VAL      |   |                | VAL     |              |    |
| Young 2014 | QUE          | 0 | 291            | PLA     | 0            | 294 |
1.8. Extrapyramidal symptoms/use of anticholinergic agent (14 studies, 4778 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|     | AOM          | 0.217 (0.024, 1.924) | 0.877 (0.251, 3.061) | 0.248 (0.020, 5.730) | 0.545 (0.052, 18.149) | 3.498 (0.674, 1.924) | 1.534 (0.540, 1.029) | 0.491 (0.235, 5.414) | 1.624 (0.487, 9.963) | 0.829 (0.069, 3.258) | 1.357 (0.565, 4.892) | 1.018 (0.212, 1.800) | 0.533 (0.241, 2.949) | 1.636 (0.908, 2.949) |
|-----|-------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| ARI | 4.043 (0.377, 43.402) | 1.143 (0.045, 28.766) | 2.515 (0.113, 55.757) | **16.130 (1.193, 218.045)** | 7.075 (0.729, 68.621) | 2.266 (0.264, 19.424) | 7.490 (0.715, 78.492) | 3.824 (0.156, 93.972) | 6.257 (0.694, 56.441) | 4.695 (0.364, 60.497) | 2.458 (0.281, 21.497) | 7.545 (0.922, 61.726) |        |        |
| ARI+LA M | 0.283 (0.020, 3.969) | 0.622 (0.050, 7.810) | 3.990 (0.652, 24.413) | 1.750 (0.881, 3.477) | 0.560 (0.195, 1.612) | 1.853 (0.404, 8.949) | 0.946 (0.066, 13.458) | 1.548 (0.459, 5.214) | 1.161 (0.187, 7.207) | 0.608 (0.196, 1.883) | 1.867 (0.620, 5.623) |        |        |
| ARI+VAL | 2.200 (0.078, 62.203) | 14.107 (0.826, 240.832) | 6.187 (0.483, 79.297) | 1.982 (0.175, 22.421) | 6.551 (0.457, 93.860) | 3.344 (0.107, 104.074) | 5.472 (0.450, 66.593) | 4.106 (0.238, 70.718) | 2.150 (0.198, 23.406) | 6.600 (0.572, 76.195) |        |        |
| ASE | 6.413 (0.411, 100.053) | 2.813 (0.246, 32.111) | 0.901 (0.089, 9.169) | 2.978 (0.243, 36.547) | 1.520 (0.055, 42.026) | 2.488 (0.233, 26.544) | 1.867 (0.125, 27.830) | 0.977 (0.094, 10.132) | 3.000 (0.308, 29.239) |        |        |
| CAR | 0.439 (0.082, 2.344) | **0.140 (0.032, 0.612)** | 0.464 (0.072, 2.988) | 0.237 (0.014, 4.153) | 0.388 (0.078, 1.927) | 0.291 (0.035, 2.417) | **0.152 (0.033, 0.706)** |        | 0.468 (0.101, 2.176) |        |        |
| LAM | 1.750 (0.881, 3.477) | **0.320 (0.143, 0.715)** | 1.059 (0.272, 4.121) | 0.541 (0.042, 7.027) | 0.884 (0.325, 2.409) | 0.664 (0.122, 3.602) | **0.347 (0.142, 0.853)** | 1.067 (0.450, 2.528) |        |        |
| LIT | 0.140 (0.032, 0.612) | 0.320 (0.139, 0.732) | **3.306 (1.056, 10.345)** | 1.688 (0.145, 19.680) | **2.762 (1.462, 5.217)** | 2.072 (0.452, 9.490) | 1.085 (0.705, 1.670) | **3.330 (2.132, 5.203)** |        |        |
|    | OLA     | 0.511 (0.037, 7.109) | 0.835 (0.243, 2.869) | 0.627 (0.104, 3.770) | 0.328 (0.101, 1.066) | 1.007 (0.353, 2.879) |
|----|---------|----------------------|----------------------|----------------------|----------------------|----------------------|
|    | PAL     | 1.636 (0.134, 19.949) | 1.228 (0.073, 20.588) | 0.643 (0.054, 7.626) | 1.973 (0.176, 22.085) |
|    | QUE     | 2.497 (1.190, 5.237) | 0.750 (0.153, 3.690) | 0.393 (0.188, 0.822) | 1.206 (0.631, 2.306) |
|    | RISLAI  | 1.087 (0.693, 1.705) | 0.524 (0.111, 2.466) | 1.607 (0.375, 6.884) | 3.069 (1.801, 5.233) |
|    | VAL     | 3.000 (0.308, 29.239) | 1.074 (0.370, 3.118) | 3.378 (2.129, 5.360) | 1.007 (0.353, 2.879) | 1.973 (0.176, 22.085) | 1.196 (0.577, 2.478) | 1.607 (0.375, 6.884) | 3.226 (1.672, 6.223) |
|    | PLA     | 1.636 (0.908, 2.949) | 7.545 (0.922, 61.726) | 3.000 (0.308, 29.239) | 1.074 (0.370, 3.118) | 3.378 (2.129, 5.360) | 1.007 (0.353, 2.879) | 1.973 (0.176, 22.085) | 1.196 (0.577, 2.478) | 1.607 (0.375, 6.884) | 3.226 (1.672, 6.223) |

**Evaluation of heterogeneity and inconsistency**

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|-----------------------------------------------------|
| 0.032                            | Low to moderate          | Q          | df | p   |
|                                  |                          | 4.660      | 4  | 0.324 |
|        | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures     |
|--------|----------------|-------------------|----------------------|-----------------------------|
|        | Ratio of risk ratios | P value           |
| LAM vs LIT | 0.320 (0.143, 0.715) | 0.320 (0.139, 0.732) | 0.331 (0.013, 8.273) | 0.964 (0.035, 26.722) | 0.983 |
| LAM vs PLA | 1.067 (0.450, 2.528) | 1.074 (0.370, 3.118) | 1.053 (0.242, 4.581) | 1.020 (0.166, 6.274) | 0.983 |
| LIT vs QUE | 2.762 (1.462, 5.217) | 2.497 (1.190, 5.237) | 3.666 (1.059, 12.694) | 0.681 (0.160, 2.892) | 0.603 |
| LIT vs VAL | 1.085 (0.705, 1.670) | 1.087 (0.693, 1.705) | 1.061 (0.235, 4.787) | 1.025 (0.213, 4.940) | 0.976 |
| LIT vs PLA | 3.330 (2.132, 5.203) | 3.378 (2.129, 5.360) | 2.719 (0.478, 15.461) | 1.242 (0.206, 7.503) | 0.813 |
| QUE vs PLA | 1.206 (0.631, 2.306) | 1.196 (0.577, 2.478) | 1.246 (0.301, 5.159) | 0.959 (0.194, 4.735) | 0.959 |
| VAL vs PLA | 3.069 (1.801, 5.233) | 3.226 (1.672, 6.223) | 2.789 (1.119, 6.950) | 1.156 (0.375, 3.562) | 0.800 |
|        | Rank 1  | Rank 2  | Rank 3  | Rank 4  | Rank 5  | Rank 6  | Rank 7  | Rank 8  | Rank 9  | Rank 10 | Rank 11 | Rank 12 | Rank 13 | Rank 14 |
|--------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| AOM    | 0.024   | 0.043   | 0.049   | 0.060   | 0.071   | 0.088   | 0.112   | 0.141   | 0.128   | 0.093   | 0.075   | 0.059   | 0.039   | 0.018   |
| ARI    | 0.008   | 0.010   | 0.016   | 0.018   | 0.019   | 0.023   | 0.035   | 0.044   | 0.059   | 0.070   | 0.080   | 0.115   | 0.261   | 0.243   |
| ARI+LAM| 0.036   | 0.047   | 0.054   | 0.059   | 0.052   | 0.059   | 0.085   | 0.098   | 0.105   | 0.098   | 0.093   | 0.084   | 0.079   | 0.052   |
| ARI+VAL| 0.013   | 0.017   | 0.017   | 0.016   | 0.014   | 0.016   | 0.019   | 0.027   | 0.032   | 0.039   | 0.050   | 0.075   | 0.154   | 0.512   |
| ASE    | 0.088   | 0.080   | 0.069   | 0.056   | 0.055   | 0.058   | 0.064   | 0.073   | 0.069   | 0.072   | 0.074   | 0.089   | 0.095   | 0.058   |
| CAR    | 0.315   | 0.177   | 0.108   | 0.070   | 0.059   | 0.058   | 0.051   | 0.045   | 0.033   | 0.029   | 0.020   | 0.018   | 0.013   | 0.003   |
| LAM    | 0.061   | 0.126   | 0.137   | 0.112   | 0.114   | 0.109   | 0.099   | 0.083   | 0.064   | 0.044   | 0.027   | 0.014   | 0.010   | 0.001   |
| LIT    | 0.000   | 0.000   | 0.000   | 0.001   | 0.003   | 0.005   | 0.014   | 0.031   | 0.074   | 0.158   | 0.236   | 0.279   | 0.167   | 0.032   |
| OLA    | 0.127   | 0.152   | 0.130   | 0.101   | 0.087   | 0.083   | 0.072   | 0.064   | 0.054   | 0.044   | 0.032   | 0.025   | 0.021   | 0.009   |
| PAL    | 0.202   | 0.118   | 0.076   | 0.064   | 0.053   | 0.056   | 0.056   | 0.055   | 0.061   | 0.054   | 0.048   | 0.057   | 0.059   | 0.042   |
| QUE    | 0.033   | 0.083   | 0.112   | 0.135   | 0.129   | 0.130   | 0.125   | 0.100   | 0.067   | 0.042   | 0.024   | 0.014   | 0.005   | 0.002   |
| RISLAI | 0.083   | 0.096   | 0.097   | 0.077   | 0.067   | 0.071   | 0.075   | 0.074   | 0.080   | 0.069   | 0.069   | 0.061   | 0.058   | 0.024   |
| VAL    | 0.007   | 0.014   | 0.022   | 0.033   | 0.042   | 0.051   | 0.075   | 0.105   | 0.147   | 0.182   | 0.171   | 0.110   | 0.039   | 0.004   |
| PLA    | 0.005   | 0.037   | 0.114   | 0.199   | 0.236   | 0.194   | 0.119   | 0.061   | 0.026   | 0.007   | 0.002   | 0.001   | 0.000   | 0.000   |
### SUCRA

| Drug   | SUCRA |
|--------|-------|
| CAR    | 0.86  |
| PLA    | 0.74  |
| OLA    | 0.68  |
| LAM    | 0.67  |
| QUE    | 0.63  |
| RISLAI | 0.54  |
| AOM    | 0.52  |
| ARI_LAM| 0.46  |
| PAL    | 0.46  |
| VAL    | 0.40  |
| ASE    | 0.36  |
| ARI_VAL| 0.26  |
| LIT    | 0.25  |
| ARI    | 0.16  |

### Comparison-adjusted funnel plot of studies of drugs versus placebo

The funnel plot is used to assess the publication bias, with each point representing a study. The SUCRA values indicate the relative efficacy of each drug compared to placebo. A higher SUCRA value suggests a greater likelihood that the drug is more effective than placebo. The funnel plot visually assesses whether the studies are symmetrically distributed around the line of no effect (0.00), with asymmetry indicating potential publication bias. This plot helps in determining if the observed effects are due to true differences or chance.
## CINeMA rating

| Comparison      | Number of studies | Within-study bias | Reporting bias     | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|-----------------|-------------------|-------------------|--------------------|--------------|-------------|---------------|-------------|-------------------|
| AOM:PLA         | 1                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI:PLA         | 1                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+LAM:LAM     | 1                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+VAL:VAL     | 1                 | Some concerns     | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| ASE:PLA         | 1                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| CAR:LIT         | 1                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LAM:LIT         | 1                 | Some concerns     | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LAM:PLA         | 1                 | Some concerns     | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:PLA         | 3                 | Some concerns     | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:QUE         | 1                 | Some concerns     | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:VAL         | 2                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| OLA:PLA         | 1                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PAL:PLA         | 1                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PLA:QUE         | 2                 | Some concerns     | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| PLA:RISLAI      | 1                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PLA:VAL         | 1                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:ARI         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:ARI+LAM     | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:ARI+VAL     | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:ASE         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:CAR         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:LAM         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:LIT         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:OLA         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:PAL         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:QUE         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:RISLAI      | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| AOM:VAL         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+LAM:LAM     | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI+VAL:VAL     | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI:ASE         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ARI:CAR         | 0                 | No concerns       | Suspected          | No concerns  | Major concerns | No concerns | No concerns | Low               |
| Combination          | Rating | Concerns | Suspected | Major Concerns | No Concerns | Very Low | Low   |
|----------------------|--------|----------|-----------|----------------|-------------|----------|-------|
| ARI:LAM              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:LIT              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:OLA              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:PAL              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:QUE              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:RISLAI           | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI:VAL              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:ARI+VAL      | 0      | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low   |
| ARI+LAM:ASE          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:CAR          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:LIT          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:OLA          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:PAL          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:PLA          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:QUE          | 0      | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:RISLAI       | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:VAL          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:ASE          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:CAR          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:LIT          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+LAM:OLA          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:PAL          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+LAM:QUE          | 0      | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+LAM:RISLAI       | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+VAL:ASE          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+VAL:CAR          | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+VAL:LAM          | 0      | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+VAL:OLA          | 0      | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+VAL:PAL          | 0      | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ARI+VAL:QUE          | 0      | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low |
| ARI+VAL:RISLAI       | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:CAR              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:LAM              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:LIT              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:OLA              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:PAL              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:QUE              | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| ASE:RISLAI           | 0      | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low   |
| Original     | Concerns Level |
|--------------|----------------|
| ASE:VAL      | Low            |
| CAR:LAM      | Low            |
| CAR:OLA      | Low            |
| CAR:PAL      | Low            |
| CAR:QUE      | Low            |
| CAR:RISLAI   | Low            |
| CAR:VAL      | Low            |
| LAM:OLA      | Low            |
| LAM:PAL      | Low            |
| LAM:QUE      | Low            |
| LAM:RISLAI   | Low            |
| LAM:VAL      | Very low       |
| LIT:OLA      | Low            |
| LIT:PAL      | Low            |
| LIT:RISLAI   | Low            |
| OLA:PAL      | Low            |
| OLA:QUE      | Low            |
| OLA:RISLAI   | Low            |
| OLA:VAL      | Low            |
| PAL:QUE      | Low            |
| PAL:RISLAI   | Low            |
| PAL:VAL      | Low            |
| QUE:RISLAI   | Low            |
| QUE:VAL      | Low            |
| RISLAI:VAL   | Low            |
1.9. Somnolence (11 studies, 4036 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half. The boldface result indicates statistical significance.

|       | ASE            | LAM          | LIT          | OLA           | PAL           | QUE           | RISLAI        | VAL           | PLA           |
|-------|----------------|--------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|
|       | 1.117 (0.063, 19.864) | 0.992 (0.059, 16.819) | 0.278 (0.015, 5.291) | 0.203 (0.006, 7.101) | 0.515 (0.029, 9.221) | 0.542 (0.026, 11.171) | 0.754 (0.044, 13.055) | 1.000 (0.061, 16.489) |
|       | 0.889 (0.474, 1.668) | 0.249 (0.082, 0.758) | 0.182 (0.018, 1.784) | 0.461 (0.186, 1.141) | 0.485 (0.131, 1.799) | 0.675 (0.308, 1.481) | 0.896 (0.465, 1.726)       |
| 0.691 (0.351, 1.359) | LIT | 0.280 (0.105, 0.743) | 0.204 (0.022, 1.888) | 0.519 (0.257, 1.047) | 0.546 (0.165, 1.806) | 0.760 (0.446, 1.294) | 1.008 (0.680, 1.492)       |
|       | 0.078 (0.004, 1.433) | OLA | 0.730 (0.068, 7.811) | 1.853 (0.596, 5.760) | 1.951 (0.770, 4.944) | 2.714 (0.956, 7.710) | 3.600 (1.448, 8.946)       |
|       | 2.015 (0.782, 5.191) | PAL | 2.540 (0.256, 25.174) | 2.674 (0.227, 31.545) | 3.720 (0.392, 35.322) | 4.933 (0.553, 44.027) |               |
| 0.394 (0.170, 0.912) | QUE |               |               |               |               |               | 1.053 (0.280, 3.965) | 1.465 (0.641, 3.347) | 1.942 (0.979, 3.854) |
|       | 0.654 (0.359, 1.188) |               |               |               |               | RISLAI | 1.391 (0.398, 4.856) | 1.845 (0.590, 5.766) |               |
| 1.000 (0.061, 16.489) |               |               |               |               | VAL |               |               |               | 1.326 (0.785, 2.241) | PLA |
| 1.338 (0.620, 2.887) |               | 1.021 (0.686, 1.521) |               |               |               |               |               |               |               |
| 3.134 (1.203, 8.166) |               |               |               |               |               |               |               |               |               |
| 4.933 (0.553, 44.027) |               |               |               |               |               |               |               |               |               |
| 1.588 (0.740, 3.407) |               |               |               |               |               |               |               |               |               |
| 2.045 (0.574, 7.294) |               |               |               |               |               |               |               |               |               |
| 1.188 (0.665, 2.124) |               |               |               |               |               |               |               |               |               |

**Evaluation of heterogeneity and inconsistency**

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|----------------------------------------------------|
| 0.061                            | Low to moderate          | Q         | df | p         |
|                                  |                          | 9.609     | 6  | 0.142     |
| Inconsistency measures | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Ratio of risk ratios | P value |
|------------------------|----------------|------------------|------------------|-------------------|--------|
| LAM vs LIT             | 0.889 (0.474, 1.668) | 0.691 (0.351, 1.359) | 4.540 (0.812, 25.378) | 0.152 (0.024, 0.967) | 0.046  |
| LAM vs PLA             | 0.896 (0.465, 1.726) | 1.338 (0.620, 2.887) | 3.050 (0.087, 1.076) | 4.382 (1.002, 19.165) | 0.050  |
| LIT vs OLA             | 0.280 (0.105, 0.743) | 0.078 (0.004, 1.433) | 0.329 (0.117, 0.928) | 0.237 (0.011, 5.205) | 0.361  |
| LIT vs QUE             | 0.519 (0.257, 1.047) | 0.394 (0.170, 0.912) | 0.985 (0.274, 3.544) | 0.400 (0.086, 1.850) | 0.241  |
| LIT vs VAL             | 0.760 (0.446, 1.294) | 0.654 (0.359, 1.188) | 1.357 (0.420, 4.382) | 0.482 (0.129, 1.797) | 0.277  |
| LIT vs PLA             | 1.008 (0.680, 1.492) | 1.021 (0.686, 1.521) | 0.608 (0.054, 6.850) | 1.680 (0.144, 19.545) | 0.679  |
| OLA vs RISLAI          | 1.951 (0.770, 4.944) | 2.015 (0.782, 5.191) | 0.793 (0.005, 117.378) | 2.541 (0.016, 410.921) | 0.719  |
| OLA vs PLA             | 3.600 (1.448, 8.946) | 3.134 (1.203, 8.166) | 13.228 (0.701, 249.560) | 0.237 (0.011, 5.205) | 0.361  |
| QUE vs PL A            | 1.942 (0.979, 3.854) | 1.588 (0.740, 3.407) | 4.478 (0.945, 21.211) | 0.355 (0.063, 2.006) | 0.241  |
| RISLAI vs PLA          | 1.845 (0.590, 5.766) | 2.045 (0.574, 7.294) | 1.209 (0.093, 15.805) | 1.692 (0.096, 29.767) | 0.719  |
| VAL vs PLA             | 1.326 (0.785, 2.241) | 1.188 (0.665, 2.124) | 2.151 (0.636, 7.282) | 0.552 (0.143, 2.132) | 0.389  |

| Rank probabilities | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 |
|--------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| ASE                | 0.625  | 0.072  | 0.037  | 0.033  | 0.046  | 0.049  | 0.044  | 0.045  | 0.050  |
| LAM                | 0.158  | 0.319  | 0.169  | 0.131  | 0.101  | 0.074  | 0.033  | 0.012  | 0.003  |
| LIT                | 0.051  | 0.204  | 0.278  | 0.231  | 0.146  | 0.070  | 0.020  | 0.002  | 0.000  |
| OLA                | 0.001  | 0.002  | 0.005  | 0.008  | 0.020  | 0.063  | 0.168  | 0.389  | 0.344  |
| PAL                | 0.038  | 0.054  | 0.038  | 0.036  | 0.047  | 0.075  | 0.129  | 0.151  | 0.433  |
| QUE                | 0.010  | 0.021  | 0.028  | 0.039  | 0.091  | 0.205  | 0.279  | 0.216  | 0.111  |
| RISLAI             | 0.058  | 0.107  | 0.074  | 0.077  | 0.119  | 0.175  | 0.201  | 0.142  | 0.048  |
| VAL                | 0.036  | 0.091  | 0.100  | 0.139  | 0.245  | 0.225  | 0.112  | 0.042  | 0.010  |
| PLA                | 0.023  | 0.131  | 0.273  | 0.307  | 0.186  | 0.065  | 0.014  | 0.002  | 0.000  |
SUCRA

|   |   |
|---|---|
| LAM | 0.76 |
| PLA | 0.74 |
| LIT | 0.73 |
| ASE | 0.63 |
| VAL | 0.54 |
| RISLAI | 0.40 |
| QUE | 0.40 |
| PAL | 0.16 |
| OLA | 0.13 |

Comparison-adjusted funnel plot of studies of drugs versus placebo
| Comparison        | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|-------------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|-------------------|
| ASE:PLA           | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LAM:LIT           | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LAM:PLA           | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:OLA           | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:PLA           | 5                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:QUE           | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:VAL           | 2                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| OLA:PLA           | 2                 | No concerns       | Suspected      | No concerns  | No concerns    | No concerns | No concerns | Moderate          |
| OLA:RISLAI        | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PAL:PLA           | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PLA:QUE           | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| PLA:RISLAI        | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PLA:VAL           | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ASE:LAM           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ASE:LIT           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ASE:OLA           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ASE:PAL           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ASE:QUE           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ASE:RISLAI        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| ASE:VAL           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LAM:OLA           | 0                 | No concerns       | Suspected      | No concerns  | No concerns    | Major concerns | No concerns | Low               |
| LAM:PAL           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LAM:QUE           | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LAM:RISLAI        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LAM:VAL           | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Very low          |
| LIT:PAL           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| LIT:RISLAI        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| OLA:PAL           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| OLA:QUE           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| OLA:VAL           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PAL:QUE           | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PAL:RISLAI        | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns | No concerns | Low               |
| PAL:VAL     | 0  | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low       |
|------------|----|-------------|-----------|-------------|----------------|-------------|-------------|-----------|
| QUE:RISLAI | 0  | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low       |
| QUE:VAL    | 0  | Some concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Very low  |
| RISLAI:VAL | 0  | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low       |
1.10. Anxiety/use of anxiolytic (11 studies, 3247 patients)

**League table**

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half. The boldface result indicates statistical significance.

| AOM | 0.996 (0.359, 2.767) | 0.628 (0.170, 2.318) | 1.734 (0.259, 11.598) | 1.276 (0.566, 2.878) | 1.290 (0.597, 2.790) | 1.668 (0.837, 3.325) | 0.891 (0.370, 2.147) | 1.974 (0.878, 4.437) | 1.156 (0.658, 2.033) |
|-----|---------------------|---------------------|----------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| ARI | 0.631 (0.147, 2.697) | 1.741 (0.235, 12.925) | 1.281 (0.455, 3.603) | 1.296 (0.476, 3.525) | 1.675 (0.654, 4.287) | 0.894 (0.301, 2.652) | 1.982 (0.706, 5.558) | 1.161 (0.495, 2.722) |
| ARI+LAM | 2.761 (0.317, 24.013) | 2.031 (0.732, 5.640) | 2.054 (0.638, 6.620) | 2.656 (0.783, 9.005) | 1.418 (0.365, 5.510) | 3.142 (0.849, 11.634) | 1.841 (0.567, 5.974) |
| ASE | 0.736 (0.109, 4.952) | 0.744 (0.113, 4.920) | 0.962 (0.150, 6.163) | 0.514 (0.074, 3.560) | 1.138 (0.169, 7.649) | 0.667 (0.109, 4.092) |
| LAM | 2.031 (0.732, 5.640) | 1.011 (0.571, 1.791) | 1.308 (0.670, 2.554) | 0.698 (0.285, 1.707) | 1.547 (0.682, 3.509) | 0.906 (0.504, 1.628) |
| LIT | 0.891 (0.492, 1.614) | 1.293 (0.726, 2.304) | 0.690 (0.293, 1.624) | 1.529 (0.708, 3.305) | 0.896 (0.530, 1.515) |
| OLA | 0.845 (0.342, 2.091) | 0.534 (0.244, 1.168) | 1.183 (0.613, 2.281) | 0.693 (0.466, 1.031) |
| PAL | 2.216 (0.909, 5.402) | 2.216 (0.909, 5.402) | 2.216 (0.909, 5.402) |
| RISLAI | 0.756 (0.302, 1.890) | 0.756 (0.302, 1.890) | 0.756 (0.302, 1.890) | 0.586 (0.328, 1.048) |
| PLA | 1.156 (0.658, 2.033) | 1.161 (0.495, 2.722) | 0.667 (0.109, 4.092) | 1.046 (0.566, 1.934) | 1.092 (0.589, 2.024) | 0.638 (0.416, 0.979) | 1.298 (0.661, 2.550) | 0.527 (0.289, 0.959) | PLA |
**Evaluation of heterogeneity and inconsistency**

Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model
--- | --- | ---
0.040 | Low to moderate | Q | df | p
5.164 | 4 | 0.271

**Inconsistency**

|       | NMA, RR (95%CI)  | Direct, RR (95%CI)  | Indirect, RR (95%CI)  | Inconsistency measures  |
|-------|------------------|---------------------|-----------------------|-------------------------|
|       | Ratio of risk ratios | P value             |
| LAM vs LIT | 1.011 (0.571, 1.791) | 0.891 (0.492, 1.614) | 4.739 (0.595, 37.743) | 0.188 (0.022, 1.627) | 0.129 |
| LAM vs PLA | 0.906 (0.504, 1.628) | 1.046 (0.566, 1.934) | 0.216 (0.031, 1.507) | 4.850 (0.631, 37.263) | 0.129 |
| LIT vs OLA | 1.293 (0.726, 2.304) | 0.845 (0.342, 2.091) | 1.730 (0.817, 3.662) | 0.488 (0.151, 1.583) | 0.232 |
| LIT vs PLA | 0.896 (0.530, 1.515) | 1.092 (0.589, 2.024) | 0.533 (0.196, 1.451) | 2.047 (0.632, 6.637) | 0.232 |
| OLA vs RISLAI | 1.183 (0.613, 2.281) | 0.756 (0.302, 1.890) | 1.896 (0.740, 4.858) | 0.399 (0.107, 1.482) | 0.170 |
| OLA vs PLA | 0.693 (0.466, 1.031) | 0.638 (0.416, 0.979) | 1.141 (0.398, 3.269) | 0.559 (0.179, 1.741) | 0.316 |
| RISLAI vs PLA | 0.586 (0.328, 1.048) | 0.527 (0.289, 0.959) | 3.198 (0.290, 35.220) | 0.165 (0.014, 1.953) | 0.153 |
### Rank probabilities

|       | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|
| AOM   | 0.026  | 0.043  | 0.054  | 0.071  | 0.081  | 0.103  | 0.135  | 0.178  | 0.178  | 0.131   |
| ARI   | 0.050  | 0.068  | 0.071  | 0.079  | 0.089  | 0.088  | 0.109  | 0.137  | 0.175  | 0.134   |
| ARI+LAM | 0.030  | 0.038  | 0.032  | 0.036  | 0.040  | 0.049  | 0.057  | 0.085  | 0.164  | 0.468   |
| ASE   | 0.428  | 0.105  | 0.075  | 0.065  | 0.054  | 0.049  | 0.045  | 0.054  | 0.064  | 0.062   |
| LAM   | 0.060  | 0.103  | 0.122  | 0.147  | 0.147  | 0.121  | 0.110  | 0.109  | 0.070  | 0.010   |
| LIT   | 0.070  | 0.117  | 0.170  | 0.190  | 0.160  | 0.113  | 0.083  | 0.060  | 0.032  | 0.006   |
| OLA   | 0.091  | 0.224  | 0.259  | 0.174  | 0.107  | 0.069  | 0.040  | 0.024  | 0.009  | 0.003   |
| PAL   | 0.026  | 0.037  | 0.044  | 0.061  | 0.074  | 0.089  | 0.111  | 0.161  | 0.227  | 0.171   |
| RISLAI| 0.219  | 0.264  | 0.160  | 0.116  | 0.082  | 0.063  | 0.040  | 0.028  | 0.022  | 0.007   |
| PLA   | 0.000  | 0.002  | 0.014  | 0.063  | 0.166  | 0.255  | 0.270  | 0.165  | 0.059  | 0.008   |
### SUCRA

| Drug   | SUCRA |
|--------|-------|
| RISLAI | 0.77  |
| OLA    | 0.75  |
| LIT    | 0.62  |
| ASE    | 0.62  |
| LAM    | 0.56  |
| PLA    | 0.42  |
| ARI    | 0.37  |
| AOM    | 0.34  |
| PAL    | 0.30  |
| ARI+LAM| 0.24  |

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**Comparison-adjusted funnel plot of studies of drugs versus placebo**

The plot shows a comparison-adjusted funnel plot of studies of drugs versus placebo. Each study is represented by a point, with the position indicating the difference between the drug and placebo effect, and the size reflecting the study's precision. The funnel shape helps to identify publication bias. The SUCRA values for each drug are listed in the table above, indicating the relative ranking of the drugs in terms of their effect size compared to placebo.
| Comparison          | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|---------------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| AOM:PLA             | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI:PLA             | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI+LAM:LAM         | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ASE:PLA             | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| LAM:LIT             | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Very low         |
| LAM:PLA             | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Very low         |
| LIT:OLA             | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| LIT:PLA             | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Very low         |
| OLA:PLA             | 2                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| OLA:RISLAI          | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| PAL:PLA             | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| PLA:RISLAI          | 2                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| AOM:ARI             | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| AOM:ARI+LAM         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| AOM:ASE             | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| AOM:LAM             | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Very low         |
| AOM:LIT             | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Very low         |
| AOM:OLA             | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| AOM:PAL             | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| AOM:RISLAI          | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI:ARI+LAM         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI:ASE             | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI:LAM             | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Very low         |
| ARI:LIT             | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI:OLA             | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI:PAL             | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI:RISLAI          | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI+LAM:ASE         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI+LAM:LIT         | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Very low         |
| ARI+LAM:OLA         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI+LAM:PAL         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Low              |
| ARI+LAM:PLA         | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | No concerns | Very low         |
| Pair       | Score | No concerns | Suspected | Major concerns | No concerns | Low | Very low |
|------------|-------|-------------|-----------|----------------|-------------|-----|----------|
| ARIN+LAM:RISLAI | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
| ASE:LAM    | 0     | Some concerns | Suspected | Major concerns | No concerns | No concerns | Very low |
| ASE:LIT    | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
| ASE:OLA    | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
| ASE:PAL    | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
| ASE:RISLAI | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
| LAM:OLA    | 0     | Some concerns | Suspected | Major concerns | No concerns | No concerns | Very low |
| LAM:PAL    | 0     | Some concerns | Suspected | Major concerns | No concerns | No concerns | Very low |
| LAM:RISLAI | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
| LIT:PAL    | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
| LIT:RISLAI | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
| OLA:PAL    | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
| PAL:RISLAI | 0     | No concerns | Suspected | Major concerns | No concerns | No concerns | Low     |
1.11. Insomnia (12 studies, 4793 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|        | AOM       | 3.000 (0.396, 22.746) | 0.953 (0.258, 3.515) | 1.140 (0.353, 3.678) | 3.042 (0.895, 10.344) | 1.092 (0.254, 4.684) | 2.814 (0.824, 9.607) | 1.333 (0.349, 5.082) | 1.000 (0.341, 2.932) |
|--------|-----------|-----------------------|----------------------|----------------------|-----------------------|----------------------|----------------------|----------------------|----------------------|
| ARI+LAM| 2.019 (0.248, 16.417) | 0.641 (0.249, 1.656) | 0.767 (0.233, 2.522) | 2.048 (0.560, 7.492) | 0.735 (0.156, 3.469) | 1.894 (0.511, 7.024) | 0.897 (0.215, 3.737) | 0.673 (0.202, 2.239) |
| ASE    | 0.318 (0.049, 2.059) | 0.380 (0.064, 2.249) | 1.014 (0.165, 6.216) | 0.364 (0.050, 2.629) | 0.938 (0.153, 5.765) | 0.444 (0.067, 2.948) | 0.333 (0.060, 1.855) |
| LAM    | 1.196 (0.583, 2.455) | 3.192 (1.317, 7.736) | 1.145 (0.335, 3.915) | 2.952 (1.194, 7.299) | 1.398 (0.481, 4.062) | 1.049 (0.501, 2.197) |
| LIT    | 0.908 (0.414, 1.992) | 2.669 (1.447, 4.920) | 0.958 (0.323, 2.837) | 2.468 (1.282, 4.752) | 1.169 (0.485, 2.817) | 0.877 (0.552, 1.395) |
| OLA    | 2.863 (1.228, 6.677) | 0.359 (0.114, 1.125) | 0.925 (0.417, 2.050) | 0.438 (0.191, 1.005) | 0.329 (0.183, 0.589) |
| PAL    | 1.933 (0.863, 4.328) | 2.578 (0.819, 8.116) | 1.221 (0.345, 4.324) | 0.916 (0.343, 2.446) | 0.355 (0.197, 0.643) |
| QUE    | 0.595 (0.236, 1.504) | 0.750 (0.338, 1.665) | 0.474 (0.178, 1.263) | 0.750 (0.338, 1.665) | 0.329 (0.177, 0.610) |
| PLA    | 1.000 (0.341, 2.932) | 0.333 (0.060, 1.855) | 1.500 (0.644, 3.496) | 0.887 (0.526, 1.493) | 0.346 (0.168, 0.713) | 0.916 (0.343, 2.446) | 0.329 (0.177, 0.610) | 0.938 (0.400, 2.195) |
### Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|-----------------------------------------------------|
| 0.116                            | Moderate to high         | 12.238                                              |
|                                  |                          | 5                                                   |
|                                  |                          | **0.032**                                            |

### Inconsistency

|                     | NMA, RR (95% CI) | Direct, RR (95% CI) | Indirect, RR (95% CI) | Inconsistency measures |
|---------------------|------------------|---------------------|-----------------------|------------------------|
|                     | Ratio of risk ratios | P value | | |
| **LAM vs LIT**      | 1.196 (0.583, 2.455) | 0.908 (0.414, 1.992) | 4.963 (0.833, 29.559) | 0.183 (0.026, 1.285) | 0.088 |
| **LAM vs PLA**      | 1.049 (0.501, 2.197) | 1.500 (0.644, 3.496) | 0.333 (0.073, 1.515) | 4.512 (0.795, 25.613) | 0.089 |
| **LIT vs OLA**      | 2.669 (1.447, 4.920) | 2.863 (1.228, 6.677) | 2.471 (1.020, 5.988) | 1.158 (0.340, 3.943) | 0.814 |
| **LIT vs QUE**      | 2.468 (1.282, 4.752) | 1.933 (0.863, 4.328) | 3.974 (1.290, 12.244) | 0.486 (0.122, 1.941) | 0.307 |
| **LIT vs PLA**      | 0.877 (0.552, 1.395) | 0.887 (0.526, 1.493) | 0.842 (0.305, 2.329) | 1.052 (0.336, 3.299) | 0.930 |
| **OLA vs RISLAI**   | 0.438 (0.191, 1.005) | 0.595 (0.236, 1.504) | 0.126 (0.019, 0.814) | 4.742 (0.589, 38.180) | 0.144 |
| **OLA vs PLA**      | 0.329 (0.183, 0.589) | 0.346 (0.168, 0.713) | 0.299 (0.111, 0.803) | 1.158 (0.340, 3.943) | 0.814 |
| **QUE vs PLA**      | 0.355 (0.197, 0.643) | 0.329 (0.177, 0.610) | 0.881 (0.107, 7.287) | 0.373 (0.041, 3.370) | 0.380 |
| **RISLAI vs PLA**   | 0.750 (0.338, 1.665) | 0.938 (0.400, 2.195) | 0.153 (0.016, 1.488) | 6.110 (0.540, 69.110) | 0.144 |
|       | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| AOM   | 0.021  | 0.031  | 0.053  | 0.103  | 0.115  | 0.101  | 0.100  | 0.095  | 0.119  | 0.263  |
| ARI+LAM | 0.051  | 0.067  | 0.109  | 0.184  | 0.136  | 0.105  | 0.080  | 0.070  | 0.095  | 0.104  |
| ASE   | 0.480  | 0.127  | 0.128  | 0.085  | 0.050  | 0.034  | 0.027  | 0.021  | 0.020  | 0.028  |
| LAM   | 0.001  | 0.005  | 0.012  | 0.037  | 0.090  | 0.131  | 0.149  | 0.171  | 0.217  | 0.188  |
| LIT   | 0.000  | 0.002  | 0.018  | 0.088  | 0.200  | 0.243  | 0.214  | 0.141  | 0.067  | 0.026  |
| OLA   | 0.265  | 0.388  | 0.234  | 0.078  | 0.023  | 0.007  | 0.003  | 0.001  | 0.001  | 0.000  |
| PAL   | 0.015  | 0.032  | 0.057  | 0.121  | 0.131  | 0.118  | 0.101  | 0.107  | 0.118  | 0.202  |
| QUE   | 0.155  | 0.322  | 0.316  | 0.129  | 0.045  | 0.016  | 0.008  | 0.006  | 0.003  | 0.001  |
| RISLAI| 0.012  | 0.026  | 0.073  | 0.170  | 0.182  | 0.149  | 0.118  | 0.095  | 0.096  | 0.078  |
| PLA   | 0.000  | 0.000  | 0.001  | 0.005  | 0.029  | 0.097  | 0.200  | 0.295  | 0.265  | 0.109  |
| SUCRA | Value |
|-------|-------|
| OLA   | 0.87  |
| QUE   | 0.81  |
| ASE   | 0.77  |
| ARI+LAM | 0.51 |
| RISLAI| 0.47  |
| LIT   | 0.39  |
| PAL   | 0.36  |
| AOM   | 0.31  |
| PLA   | 0.27  |
| LAM   | 0.25  |
| Comparison      | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|-----------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| AOM:PLA         | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI+LAM:LAM     | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ASE:PLA         | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| LAM:LIT         | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | No concerns   | Very low         |
| LAM:PLA         | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | No concerns   | Very low         |
| LIT:OLA         | 1                 | No concerns       | Suspected      | No concerns  | No concerns   | Major concerns | No concerns   | Low              |
| LIT:PLA         | 4                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | No concerns   | Very low         |
| LIT:QUE         | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | No concerns   | Very low         |
| OLA:PLA         | 2                 | No concerns       | Suspected      | No concerns  | No concerns   | No concerns   | No concerns   | Low              |
| OLA:RISLAI      | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | No concerns   | Low              |
| PAL:PLA         | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| PLA:QUE         | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | No concerns   | Very low         |
| PLA:RISLAI      | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | No concerns   | Low              |
| AOM:ARI+LAM     | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| AOM:ASE         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| AOM:LAM         | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| AOM:LIT         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| AOM:OLA         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| AOM:PAL         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| AOM:QUE         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| AOM:RISLAI      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI+LAM:ASE     | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI+LAM:LIT     | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI+LAM:OLA     | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI+LAM:PAL     | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI+LAM:PLA     | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI+LAM:QUE     | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI+LAM:RISLAI  | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ASE:PLA         | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ASE:QUE         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ASE:OLA         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ASE:PAL         | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
|   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|
| ASE:QUE | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ASE:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LAM:OLA | 0 | No concerns | Suspected | No concerns | No concerns | Major concerns | Major concerns | Very low |
| LAM:PAL | 0 | Some concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LAM:QUE | 0 | Some concerns | Suspected | No concerns | No concerns | Major concerns | Major concerns | Very low |
| LAM:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT:PAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| OLA:PAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| OLA:QUE | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| PAL:QUE | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| PAL:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| QUE:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
1.12. Prolactin-related adverse events (3 studies, 838 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half. The boldface result indicates statistical significance.

|          | PAL            | 1.638 (0.169, 15.881) | 7.892 (1.000, 62.321) |
|----------|----------------|-----------------------|-----------------------|
|          | RISLAI         | 4.819 (1.875, 12.389) |                       |
|          | PLA            | 7.892 (1.000, 62.321) | 4.819 (1.875, 12.389) |

Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|-----------------------------------------------------|
| 0.01                             | Low                      | Not estimate                                        |

Rank probabilities

|          | Rank 1 | Rank 2 | Rank 3 |
|----------|--------|--------|--------|
| PAL      | 0.080  | 0.355  | 0.565  |
| RISLAI   | 0.038  | 0.533  | 0.429  |
| PLA      | 0.882  | 0.112  | 0.006  |
SUCRA

|     | PLA | 0.97 |
|-----|-----|------|
|     | RISLAI | 0.34 |
|     | PAL   | 0.19 |

Comparison-adjusted funnel plot of studies of drugs versus placebo
# CINeMA rating

| Comparison       | Number of studies | Within-study bias | Reporting bias  | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------------|-------------------|-------------------|-----------------|--------------|-------------|---------------|-------------|------------------|
| PAL:PLA          | 1                 | No concerns       | Suspected       | No concerns  | Major concerns | No concerns | Major concerns | Very low         |
| PLA:RISLAI       | 2                 | No concerns       | Suspected       | No concerns  | No concerns  | Major concerns | Major concerns | Very low         |
| PAL:RISLAI       | 0                 | No concerns       | Suspected       | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
1.13. Dry mouth (7 studies, 2117 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|     | ARI           | ASE          | CAR          | LIT         | OLA         | PAL          | QUE         | VAL         | PLA         |
|-----|---------------|--------------|--------------|-------------|-------------|--------------|-------------|-------------|-------------|
|     | 6.468 (0.076, 546.864) | 6.021 (0.569, 63.669) | 3.234 (0.336, 31.122) | 2.675 (0.130, 55.009) | 13.112 (0.547, 314.442) | 1.829 (0.172, 19.470) | 8.187 (0.833, 80.463) | 6.468 (0.797, 52.510) |
|     | 0.931 (0.016, 53.958)   | 0.500 (0.009, 27.459) | 0.414 (0.005, 36.459) | 2.027 (0.021, 198.522) | 0.283 (0.005, 16.456) | 1.266 (0.023, 70.351) | 1.000 (0.020, 50.009) |
|     | 0.537 (0.278, 1.039)          | 0.444 (0.039, 5.076) | 2.178 (0.158, 30.039) | 0.304 (0.065, 1.423) | 1.360 (0.501, 3.691) | 1.074 (0.363, 3.178) |
|     | 0.827 (0.079, 8.629)        | 4.054 (0.320, 51.408) | 0.566 (0.140, 2.285) | 2.532 (1.196, 5.359) | 2.000 (0.845, 4.731) |
|     | 4.901 (0.193, 124.549)      | 0.684 (0.059, 7.863) | 3.061 (0.288, 32.580) | 2.418 (0.273, 21.409) |
|     | 0.139 (0.010, 1.936)        | 0.625 (0.048, 8.068) | 0.493 (0.045, 5.382) |
|     | 2.532 (1.196, 5.359)        | 4.476 (1.071, 18.707) | 3.536 (1.178, 10.615) |
|     | 6.468 (0.797, 52.510)       | 1.000 (0.020, 50.009) | 2.000 (0.845, 4.731) | 2.418 (0.273, 21.409) | 0.493 (0.045, 5.382) | 3.536 (1.178, 10.615) | 0.790 (0.316, 1.972) | PLA         |

Evaluation of heterogeneity and inconsistency

| Between study variance (\(\tau^2\)) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|-------------------------------------|-------------------------|----------------------------------------------------|
| 0.15                                 | High                    | Not estimate                                       |
|   | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 |
|---|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| ARI | 0.001  | 0.018  | 0.033  | 0.042  | 0.062  | 0.077  | 0.123  | 0.216  | 0.428  |
| ASE | 0.923  | 0.036  | 0.010  | 0.006  | 0.006  | 0.004  | 0.004  | 0.004  | 0.007  |
| CAR | 0.008  | 0.108  | 0.167  | 0.166  | 0.146  | 0.150  | 0.113  | 0.081  | 0.061  |
| LIT | 0.001  | 0.007  | 0.039  | 0.081  | 0.127  | 0.205  | 0.267  | 0.194  | 0.081  |
| OLA | 0.005  | 0.091  | 0.155  | 0.109  | 0.116  | 0.115  | 0.147  | 0.138  | 0.124  |
| PAL | 0.055  | 0.558  | 0.137  | 0.072  | 0.054  | 0.043  | 0.039  | 0.029  | 0.014  |
| QUE | 0.001  | 0.017  | 0.036  | 0.046  | 0.072  | 0.105  | 0.162  | 0.289  | 0.272  |
| VAL | 0.007  | 0.146  | 0.286  | 0.216  | 0.145  | 0.093  | 0.063  | 0.031  | 0.013  |
| PLA | 0.000  | 0.019  | 0.137  | 0.263  | 0.271  | 0.208  | 0.082  | 0.017  | 0.002  |
| Drug | SUCRA |
|------|-------|
| PAL  | 0.77  |
| VAL  | 0.71  |
| CAR  | 0.67  |
| PLA  | 0.66  |
| LIT  | 0.42  |
| OLA  | 0.39  |
| ASE  | 0.34  |
| QUE  | 0.33  |
| ARI  | 0.21  |
| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|------------------|-------------------|----------------|--------------|-------------|---------------|-------------|-------------------|
| ARI:PLA    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ASE:PLA    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| CAR:LIT    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LIT:PLA    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LIT:VAL    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| OLA:PLA    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| PAL:PLA    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| PLA:QUE    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | Major concerns | Major concerns | Very low          |
| PLA:VAL    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:ASE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:CAR    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:LIT    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:OLA    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:PAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:QUE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:VAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ASE:CAR    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ASE:LIT    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ASE:OLA    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ASE:PAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ASE:QUE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ASE:VAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| CAR:OLA    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| CAR:PAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| CAR:PLA    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| CAR:QUE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| CAR:VAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LIT:OLA    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LIT:PAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LIT:QUE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| OLA:PAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| OLA:QUE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
|                | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
|----------------|---|-------------|-----------|-------------|---------------|-------------|---------------|---------|
| OLA:VAL        |   |             |           |             |               |             |               |         |
| PAL:QUE        |   |             |           |             |               |             |               |         |
| PAL:VAL        |   |             |           |             |               |             |               |         |
| QUE:VAL        |   |             |           |             |               |             |               |         |
1.14. Headache (13 studies, 4702 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|          | AOM        | ARI+LAM    | ARI+VAL    | ASE        | LAM        | LIT        | LIT        | OLA        | PAL        |
|----------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
|          | (0.136, 3.118) | (0.004, 7.644) | (0.034, 2.603) | (0.106, 1.329) | (0.106, 1.600) | (0.138, 4.507) | (0.112, 1.414) | (0.336, 15.981) | (0.133, 1.485) |
| AOM      | 0.650      | 0.169      | 0.296      | 0.375      | 0.372      | 0.404      | 0.788      | 0.398      | 2.316      |
|          | (0.136, 3.118) | (0.004, 7.644) | (0.034, 2.603) | (0.106, 1.329) | (0.106, 1.600) | (0.138, 4.507) | (0.112, 1.414) | (0.336, 15.981) | (0.133, 1.485) |
|          | 0.259      | 0.456      | 0.577      | 0.572      | 0.622      | 1.212      | 0.611      | 3.560      | 0.036      |
|          | (0.006, 10.961) | (0.058, 3.595) | (0.229, 1.456) | (0.205, 1.600) | (0.190, 2.033) | (0.243, 6.049) | (0.211, 1.771) | (0.586, 21.646) | (0.003, 1.209) |
|          | 1.757      | 2.225      | 2.066      | 2.397      | 4.674      | 2.357      | 13.732     | 0.215      | 2.635      |
|          | (0.031, 100.263) | (0.059, 83.730) | (0.060, 80.770) | (0.062, 93.270) | (0.101, 215.422) | (0.063, 88.668) | (0.275, 686.084) | (0.025, 1.815) | (0.071, 98.190) |
|          | 1.266      | 1.256      | 1.364      | 2.661      | 1.342      | 7.816      | 0.122      | 0.150      | 1.184      |
|          | (0.200, 8.028) | (0.199, 7.928) | (0.199, 9.348) | (0.294, 24.071) | (0.211, 8.531) | (0.742, 82.294) | (0.004, 3.801) | (0.246, 9.142) | (0.811, 1.730) |
|          | 0.577      | 0.992      | 1.077      | 2.101      | 1.060      | 6.172      | 0.097      | 0.118      | 1.194      |
|          | (0.229, 1.456) | (0.634, 1.552) | (0.514, 2.257) | (0.564, 7.820) | (0.628, 1.789) | (1.311, 29.058) | (0.005, 1.818) | (0.835, 1.708) | (0.835, 1.708) |
|          | 1.165      | 1.086      | 2.118      | 1.068      | 6.223      | 0.972      | 0.909      | 1.099      |
|          | (0.665, 2.042) | (0.558, 2.116) | (0.573, 7.839) | (0.686, 1.665) | (1.349, 28.709) | (0.005, 1.758) | (0.005, 1.758) | (0.568, 2.130) | (0.109, 1.984) |
|          | 1.239      | 1.950      | 0.984      | 2.938      | 0.504      | 2.046      | 0.564      |
|          | (0.488, 3.145) | (0.471, 8.081) | (0.468, 2.066) | (0.412, 20.947) | (0.135, 1.885) | (0.002, 1.108) | (0.160, 1.984) |
Evaluation of heterogeneity and inconsistency

| Between study variance ($r^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|--------------------------------|--------------------------|---------------------------------------------------|
| 0.033                          | Low to moderate          | Q 1.576 df 4 p 0.813                              |
| Inconsistency | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures |
|---------------|----------------|--------------------|---------------------|-----------------------|
|               | Ratio of risk ratios | P value |                     |                       |
| LAM vs LIT    | 0.992 (0.634, 1.552) | 1.165 (0.665, 2.042) | 0.748 (0.356, 1.571) | 1.559 (0.615, 3.954) | 0.350 |
| LAM vs PLA    | 1.184 (0.811, 1.730) | 1.088 (0.733, 1.616) | 3.045 (0.813, 11.398) | 0.357 (0.090, 1.418) | 0.143 |
| LIT vs OLA    | 1.086 (0.558, 2.116) | 1.239 (0.488, 3.145) | 0.946 (0.364, 2.457) | 1.311 (0.345, 4.975) | 0.691 |
| LIT vs QUE    | 1.068 (0.686, 1.665) | 1.289 (0.749, 2.217) | 0.733 (0.339, 1.582) | 1.759 (0.686, 4.512) | 0.240 |
| LIT vs PLA    | 1.194 (0.835, 1.708) | 1.071 (0.719, 1.596) | 1.882 (0.833, 4.257) | 0.569 (0.230, 1.411) | 0.224 |
| OLA vs RISLAI | 5.729 (1.283, 25.577) | 6.046 (1.323, 27.630) | 1.035 (0.000, 5426.773) | 5.840 (0.001, 34992.884) | 0.691 |
| OLA vs PLA    | 1.099 (0.568, 2.130) | 1.237 (0.513, 2.979) | 0.943 (0.346, 2.572) | 1.311 (0.345, 4.975) | 0.691 |
| QUE vs PLA    | 1.118 (0.755, 1.656) | 1.208 (0.800, 1.823) | 0.509 (0.137, 1.894) | 2.374 (0.599, 9.413) | 0.219 |
| RISLAI vs PLA | 0.192 (0.042, 0.867) | 0.205 (0.044, 0.955) | 0.044 (0.000, 72.132) | 4.633 (0.002, 8872.395) | 0.691 |
|       | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 | Rank 11 | Rank 12 |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|---------|---------|
| AOM   | 0.134  | 0.319  | 0.229  | 0.126  | 0.064  | 0.034  | 0.022  | 0.017  | 0.018  | 0.024   | 0.010   | 0.004   |
| ARI+LAM | 0.020 | 0.082  | 0.159  | 0.188  | 0.140  | 0.077  | 0.060  | 0.062  | 0.070  | 0.079   | 0.042   | 0.020   |
| ARI+VAL | 0.043 | 0.057  | 0.057  | 0.056  | 0.042  | 0.031  | 0.024  | 0.025  | 0.033  | 0.077   | 0.434   | 0.123   |
| ASE   | 0.030  | 0.081  | 0.105  | 0.114  | 0.085  | 0.054  | 0.045  | 0.046  | 0.057  | 0.193   | 0.109   | 0.082   |
| LAM   | 0.000  | 0.001  | 0.006  | 0.025  | 0.059  | 0.093  | 0.133  | 0.173  | 0.226  | 0.191   | 0.074   | 0.020   |
| LIT   | 0.000  | 0.005  | 0.020  | 0.054  | 0.107  | 0.154  | 0.175  | 0.194  | 0.164  | 0.099   | 0.026   | 0.004   |
| OLA   | 0.001  | 0.021  | 0.070  | 0.139  | 0.158  | 0.141  | 0.102  | 0.101  | 0.106  | 0.102   | 0.046   | 0.014   |
| PAL   | 0.094  | 0.229  | 0.240  | 0.151  | 0.082  | 0.042  | 0.031  | 0.032  | 0.036  | 0.037   | 0.018   | 0.009   |
| QUE   | 0.001  | 0.006  | 0.027  | 0.070  | 0.110  | 0.134  | 0.153  | 0.154  | 0.158  | 0.122   | 0.050   | 0.016   |
| RISLAI | 0.677 | 0.197  | 0.074  | 0.027  | 0.011  | 0.006  | 0.003  | 0.002  | 0.001  | 0.001   | 0.001   | 0.001   |
| VAL   | 0.000  | 0.002  | 0.005  | 0.010  | 0.014  | 0.015  | 0.013  | 0.014  | 0.014  | 0.031   | 0.177   | 0.707   |
| PLA   | 0.000  | 0.001  | 0.008  | 0.040  | 0.130  | 0.219  | 0.239  | 0.184  | 0.119  | 0.045   | 0.015   | 0.002   |
| Treatment   | SUCRA |
|------------|-------|
| RISLAI     | 0.95  |
| AOM        | 0.80  |
| PAL        | 0.73  |
| ARI+LAM    | 0.65  |
| PLA        | 0.54  |
| OLA        | 0.50  |
| QUE        | 0.47  |
| LIT        | 0.47  |
| ASE        | 0.40  |
| LAM        | 0.38  |
| ARI+VAL    | 0.11  |
| VAL        | 0.01  |
| Comparison          | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|--------------------|------------------|------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| AOM:PLA            | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| ARI+LAM:PLA       | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| ARI+VAL:VAL       | 1                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| ASE:PLA            | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| LAM:LIT            | 2                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| LAM:PLA            | 3                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| LIT:OLA            | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| LIT:PLA            | 3                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| LIT:QUE            | 1                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| LIT:VAL            | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| OLA:PLA            | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| OLA:RISLAI         | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| PAL:PLA            | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| PLA:QUE            | 2                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| PLA:RISLAI         | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| AOM:ARI+LAM       | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| AOM:ARI+VAL       | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| AOM:ASE            | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| AOM:LAM            | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| AOM:LIT            | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| AOM:OLA            | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| AOM:PAL            | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| AOM:QUE            | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| AOM:RISLAI         | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| AOM:VAL            | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| ARI+LAM:ARI+VAL    | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| ARI+LAM:ASE        | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| ARI+LAM:LIT        | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| ARI+LAM:OLA        | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| ARI+LAM:PAL        | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Low              |
| ARI+LAM:PLA        | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| ARI+LAM:QUE        | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | No concerns | Very low         |
| Combination          | Concerns | Suspected | Major Concerns | No Concerns | Major Concerns | Low       |
|----------------------|----------|-----------|----------------|-------------|----------------|-----------|
| ARI+LAM:RISLAI       | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ARI+LAM:VAL          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ARI+VAL:ASE          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ARI+VAL:LAM          | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ARI+VAL:LIT          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| ARI+VAL:OLA          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ARI+VAL:PAL          | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ARI+VAL:PLA          | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| ARI+VAL:QUE          | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| ARI+VAL:RISLAI       | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ASE:LAM              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ASE:LIT              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ASE:OLA              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ASE:PAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ASE:QUE              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ASE:RISLAI           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| ASE:VAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| LAM:OLA              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| LAM:PAL              | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM:QUE              | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LAM:RISLAI           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| LAM:VAL              | 0        | Some concerns | No concerns | Major concerns | No concerns | No concerns | Very low  |
| LIT:PAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| LIT:RISLAI           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| OLA:PAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| OLA:QUE              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| OLA:RISLAI           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| OLA:VAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| PAL:QUE              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| PAL:RISLAI           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| PAL:VAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| PLA:VAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| QUE:RISLAI           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| QUE:VAL              | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
| RISLAI:VAL           | 0        | No concerns | No concerns | Major concerns | No concerns | No concerns | Low       |
1.15. Increased weight (13 studies, 3558 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|          | AOM        |       |       |       |       |       |       |       |       |       |       |       |
|----------|------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|          | 0.333      | 0.531 | 1.218 | 1.050 | 0.376 | 1.102 | 1.143 | 0.699 | 0.588 | 0.642 | 1.353 |       |
|          | (0.006, 17.786) |       |       |       |       |       |       |       |       |       |       | (0.090, 20.344) |
|          | 3.660      | 1.595 |       |       |       |       |       |       |       |       |       |       |
|          | (0.065, 175.107) |       |       |       |       |       |       |       |       |       |       |       |
|          | 1.079      | 2.924 |       |       |       |       |       |       |       |       |       |       |
|          | (0.007, 65.733) |       |       |       |       |       |       |       |       |       |       | (0.023, 233.061) |
|          | 2.076      | 1.978 |       |       |       |       |       |       |       |       |       |       |
|          | (0.007, 74.769) |       |       |       |       |       |       |       |       |       |       | (0.060, 65.733) |
|          | 2.154      | 0.862 |       |       |       |       |       |       |       |       |       |       |
|          | (0.007, 94.679) |       |       |       |       |       |       |       |       |       |       | (0.026, 28.219) |
|          | 0.939      | 0.359 |       |       |       |       |       |       |       |       |       |       |
|          | (0.034, 24.335) |       |       |       |       |       |       |       |       |       |       | (0.017, 7.720) |
|          | 0.574      | 1.050 |       |       |       |       |       |       |       |       |       |       |
|          | (0.018, 47.660) |       |       |       |       |       |       |       |       |       |       | (0.003, 32.217) |
|          | 0.666      | 0.359 |       |       |       |       |       |       |       |       |       |       |
|          | (0.021, 20.901) |       |       |       |       |       |       |       |       |       |       | (0.017, 7.720) |
|          | 1.562      | 0.724 |       |       |       |       |       |       |       |       |       |       |
|          | (0.027, 91.067) |       |       |       |       |       |       |       |       |       |       | (0.046, 11.479) |
|          | 1.856      | 0.359 |       |       |       |       |       |       |       |       |       |       |
|          | (0.018, 135.046) |       |       |       |       |       |       |       |       |       |       | (0.017, 7.720) |
|          | 0.534      | 0.724 |       |       |       |       |       |       |       |       |       |       |
|          | (0.059, 4.866) |       |       |       |       |       |       |       |       |       |       | (0.039, 27.478) |
|          | 0.611      | 0.724 |       |       |       |       |       |       |       |       |       |       |
|          | (0.012, 29.919) |       |       |       |       |       |       |       |       |       |       | (0.046, 11.479) |
|          | 0.514      | 0.724 |       |       |       |       |       |       |       |       |       |       |
|          | (0.018, 14.611) |       |       |       |       |       |       |       |       |       |       | (0.046, 11.479) |
|          | 0.562      | 0.724 |       |       |       |       |       |       |       |       |       |       |
|          | (0.014, 22.200) |       |       |       |       |       |       |       |       |       |       | (0.046, 11.479) |
|          | 1.184      | 0.724 |       |       |       |       |       |       |       |       |       |       |
|          | (0.074, 18.863) |       |       |       |       |       |       |       |       |       |       | (0.046, 11.479) |
### Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|---------------------------------------------------|
| 1.825                            | High                     | Q 31.210 df 4 p **0.000**                           |
| Inconsistency | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures |
|---------------|----------------|-------------------|---------------------|----------------------|
|               |                |                   |                     | Ratio of risk ratios | P value               |
| LIT vs OLA    | 1.050 (0.126, 8.779) | 0.724 (0.046, 11.479) | 1.794 (0.065, 49.630) | 0.404 (0.005, 30.341) | 0.681                |
| LIT vs VAL    | 0.611 (0.073, 5.152)  | 0.691 (0.076, 6.288)  | 0.118 (0.000, 394.729) | 5.846 (0.001, 26238.944) | 0.681                |
| LIT vs PLA    | 1.289 (0.158, 10.521) | 1.714 (0.105, 27.983) | 0.890 (0.037, 21.484)  | 1.927 (0.028, 133.113)  | 0.761                |
| OLA vs RISLAI | 0.534 (0.059, 4.886)  | 0.294 (0.018, 4.681)  | 1.524 (0.039, 59.985)   | 0.404 (0.005, 30.341) | 0.681                |
| OLA vs PLA    | 1.228 (0.213, 7.090)  | 0.874 (0.114, 6.693)  | 3.263 (0.103, 103.069) | 0.005 (0.000, 6.020) | 0.143                |
| RISLAI vs PLA | 2.301 (0.351, 15.085) | 1.539 (0.218, 10.879) | 309.978 (0.336, 285614.992) | 5.846 (0.001, 26238.944) | 0.681                |
| VAL vs PLA    | 2.108 (0.187, 23.708) | 2.801 (0.178, 44.089) | 0.811 (0.005, 127.218) | 3.455 (0.011, 1094.661) | 0.673                |

| Rank probabilities |
|--------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                   | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 | Rank 11 | Rank 12 |
| AOM                | 0.123  | 0.113  | 0.086  | 0.077 | 0.069 | 0.072 | 0.079 | 0.079 | 0.085 | 0.079 | 0.081 | 0.058 |
| ARI                | 0.039  | 0.041  | 0.038  | 0.038 | 0.045 | 0.047 | 0.058 | 0.077 | 0.093 | 0.119 | 0.162 | 0.243 |
| ARI+VAL            | 0.097  | 0.069  | 0.055  | 0.047 | 0.048 | 0.052 | 0.062 | 0.068 | 0.084 | 0.098 | 0.136 | 0.184 |
| ASE                | 0.200  | 0.126  | 0.091  | 0.070 | 0.071 | 0.073 | 0.065 | 0.069 | 0.065 | 0.066 | 0.059 | 0.046 |
| LIT                | 0.046  | 0.095  | 0.101  | 0.112 | 0.112 | 0.113 | 0.114 | 0.114 | 0.088 | 0.064 | 0.033 | 0.008 |
| LIT+OXC            | 0.088  | 0.062  | 0.054  | 0.050 | 0.041 | 0.053 | 0.057 | 0.067 | 0.084 | 0.097 | 0.130 | 0.219 |
| OLA                | 0.076  | 0.112  | 0.126  | 0.124 | 0.131 | 0.115 | 0.106 | 0.084 | 0.061 | 0.039 | 0.020 | 0.004 |
| PAL                | 0.178  | 0.117  | 0.086  | 0.074 | 0.069 | 0.074 | 0.071 | 0.070 | 0.071 | 0.074 | 0.064 | 0.053 |
| QUE                | 0.083  | 0.078  | 0.070  | 0.061 | 0.066 | 0.068 | 0.076 | 0.085 | 0.091 | 0.110 | 0.114 | 0.098 |
| RISLAI             | 0.017  | 0.039  | 0.051  | 0.063 | 0.077 | 0.095 | 0.106 | 0.118 | 0.129 | 0.133 | 0.111 | 0.060 |
| VAL                | 0.033  | 0.064  | 0.079  | 0.078 | 0.081 | 0.093 | 0.102 | 0.114 | 0.124 | 0.115 | 0.089 | 0.028 |
| PLA                | 0.020  | 0.084  | 0.163  | 0.206 | 0.190 | 0.146 | 0.104 | 0.056 | 0.025 | 0.006 | 0.001 | 0.000 |
| SUCRA | Value |
|-------|-------|
| PLA   | 0.69  |
| OLA   | 0.62  |
| ASE   | 0.61  |
| LIT   | 0.60  |
| PAL   | 0.60  |
| AOM   | 0.56  |
| QUE   | 0.48  |
| VAL   | 0.43  |
| RISLAI | 0.42 |
| ARI+VAL | 0.40 |
| LIT+OXC | 0.32 |
| ARI   | 0.29  |

Comparison-adjusted funnel plot of studies of drugs versus placebo

Effect centered at comparison-specific pooled effect
| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|------------------|------------------|----------------|--------------|-------------|---------------|-------------|-------------------|
| AOM:PLA | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI:PLA | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI+VAL:VAL | 1 | Some concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ASE:PLA | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT:LIT+OXC | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT:OLA | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT:PLA | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| LIT:VAL | 2 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| OLA:PLA | 2 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| OLA:RISLAI | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| PAL:PLA | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| PLA:QUE | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| PLA:RISLAI | 2 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| PLA:VAL | 1 | No concerns | Suspected | No concerns | Major concerns | No concerns | No concerns | Low |
| AOM:ARI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| AOM:ARI+VAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| AOM:ASE | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| AOM:LIT | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| AOM:LIT+OXC | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| AOM:OLA | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| AOM:PAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| AOM:QUE | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| AOM:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| AOM:VAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI:ARI+VAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI:ASE | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI:LIT | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI:LIT+OXC | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI:OLA | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI:PAL | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI:QUE | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI:RISLAI | 0 | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| Combination         | Score | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
|---------------------|-------|-------------|-----------|-------------|----------------|-------------|----------------|---------|
| ARI:VAL             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI+VAL:ASE         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI+VAL:LIT         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI+VAL:LIT+OXC     | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI+VAL:OLA         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI+VAL:PAL         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI+VAL:QUE         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ARI+VAL:RISLAI      | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ASE:LIT             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ASE:LIT+OXC         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ASE:OLA             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ASE:PAL             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ASE:QUE             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ASE:RISLAI          | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| ASE:VAL             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT:PAL             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT:QUE             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT:RISLAI          | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT+OXC:OLA         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT+OXC:PAL         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT+OXC:QUE         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT+OXC:RISLAI      | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| LIT+OXC:VAL         | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| OLA:PAL             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| OLA:QUE             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| OLA:VAL             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| PAL:QUE             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| PAL:RISLAI          | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| PAL:VAL             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| QUE:RISLAI          | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| QUE:VAL             | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
| RISLAI:VAL          | 0     | No concerns | Suspected | No concerns | Major concerns | No concerns | Major concerns | Very low |
1.16. Nausea (9 studies, 3929 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

| ASE    | 2.503 (0.101, 62.253) | 1.881 (0.077, 46.132) | 15.255 (0.337, 689.661) | 6.082 (0.113, 327.635) | 4.354 (0.174, 108.984) | 2.029 (0.082, 49.999) | 3.000 (0.123, 72.945) |
|--------|-----------------------|-----------------------|-------------------------|------------------------|------------------------|------------------------|------------------------|
| LAM    | 0.751 (0.514, 1.099)  | 6.095 (0.743, 50.009) | 2.430 (0.216, 27.311)  | 1.739 (1.001, 3.021)  | 0.811 (0.523, 1.258)  | 1.198 (0.820, 1.752)  |
|        | 0.718 (0.458, 1.127)  | LIT                   | 8.112 (1.023, 64.303)  | 3.234 (0.293, 35.698) | 2.315 (1.494, 3.587)  | 1.079 (0.830, 1.404)  | 1.595 (1.258, 2.023)  |
|        | 8.112 (1.023, 64.303) | OLA                   | 0.399 (0.017, 9.496)   | 0.285 (0.034, 2.368)  | 0.133 (0.017, 1.072)  | 0.197 (0.024, 1.580)  |
|        |                      |                       |                         |                        |                        |                        |                        |
|        |                      |                       |                         |                        |                        |                        |                        |
|        |                      |                       |                         |                        |                        |                        |                        |
|        | 2.846 (1.697, 4.772) | PAL                   | 0.716 (0.063, 8.117)   | 0.334 (0.030, 3.705)  | 0.493 (0.045, 5.382)  |
|        |                      | QUE                   | 0.466 (0.286, 0.759)   | 0.689 (0.448, 1.061)  |
|        |                      |                       |                          |                        |                        |                        |                        |
|        |                      |                       |                          |                        |                        |                        |                        |
|        |                      |                       |                          |                        |                        |                        |                        |
|        | 3.000 (0.123, 72.945) | 1.220 (0.790, 1.882)  | 1.540 (1.206, 1.966)   | 0.493 (0.045, 5.382)  | 0.709 (0.450, 1.117)  | 1.369 (0.969, 1.935)  |
|        |                      |                       |                          |                        |                        |                        |                        |
|        |                      |                       |                          |                        |                        |                        |                        |
|        |                      |                       |                          |                        |                        |                        |                        |
|        |                      |                       |                          |                        |                        |                        |                        |
|        |                      |                       |                          |                        |                        |                        |                        |

Evaluation of heterogeneity and inconsistency

| Between study variance (τ²) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|-----------------------------|--------------------------|----------------------------------------------------|
| Q                           | df                       | p                                                  |
| 0.01                        | Low                      | 3.188                                              | 4                      | 0.527                  |
### Inconsistency

|                | NMA, RR (95%CI)     | Direct, RR (95%CI)   | Indirect, RR (95%CI) | Inconsistency measures |
|----------------|---------------------|----------------------|----------------------|------------------------|
|                |                     |                      |                      | Ratio of risk ratios    | P value               |
| LAM vs LIT     | 0.751 (0.514, 1.099)| 0.718 (0.458, 1.127) | 0.840 (0.413, 1.705) | 0.855 (0.369, 1.980)   | 0.715                 |
| LAM vs PLA     | 1.198 (0.820, 1.752)| 1.220 (0.790, 1.882) | 1.132 (0.517, 2.476) | 1.078 (0.440, 2.637)   | 0.870                 |
| LIT vs QUE     | 2.315 (1.494, 3.587)| 2.846 (1.697, 4.772) | 1.369 (0.600, 3.123) | 2.079 (0.786, 5.503)   | 0.141                 |
| LIT vs VAL     | 1.079 (0.830, 1.404)| 1.032 (0.777, 1.372) | 1.399 (0.702, 2.788) | 0.738 (0.350, 1.556)   | 0.425                 |
| LIT vs PLA     | 1.595 (1.258, 2.023)| 1.540 (1.206, 1.966) | 2.909 (1.064, 7.953) | 0.529 (0.188, 1.490)   | 0.228                 |
| QUE vs PLA     | 0.689 (0.448, 1.061)| 0.709 (0.450, 1.117) | 0.533 (0.136, 2.095) | 1.329 (0.314, 5.618)   | 0.699                 |
| VAL vs PLA     | 1.478 (1.106, 1.976)| 1.369 (0.969, 1.935) | 1.774 (1.040, 3.027) | 0.772 (0.408, 1.458)   | 0.425                 |

### Rank probabilities table

|                | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 |
|----------------|--------|--------|--------|--------|--------|--------|--------|--------|
| ASE            | 0.094  | 0.164  | 0.175  | 0.070  | 0.047  | 0.049  | 0.041  | 0.360  |
| LAM            | 0.000  | 0.010  | 0.062  | 0.185  | 0.342  | 0.280  | 0.095  | 0.026  |
| LIT            | 0.000  | 0.000  | 0.001  | 0.004  | 0.026  | 0.181  | 0.440  | 0.349  |
| OLA            | 0.586  | 0.310  | 0.073  | 0.013  | 0.007  | 0.006  | 0.002  | 0.002  |
| PAL            | 0.312  | 0.358  | 0.150  | 0.051  | 0.029  | 0.028  | 0.028  | 0.046  |
| QUE            | 0.007  | 0.150  | 0.461  | 0.301  | 0.052  | 0.020  | 0.007  | 0.002  |
| VAL            | 0.000  | 0.003  | 0.012  | 0.035  | 0.094  | 0.273  | 0.371  | 0.214  |
| PLA            | 0.000  | 0.005  | 0.066  | 0.342  | 0.405  | 0.163  | 0.018  | 0.001  |
| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| ASE:PLA    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| LAM:LIT    | 2                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Very low         |
| LAM:PLA    | 3                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Very low         |
| LIT:OLA    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| LIT:PLA    | 4                | Some concerns     | Suspected      | No concerns  | No concerns    | No concerns    | No concerns   | Low              |
| LIT:QUE    | 1                | Some concerns     | Suspected      | No concerns  | No concerns    | No concerns    | No concerns   | Low              |
| LIT:VAL    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| PAL:PLA    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| PLA:QUE    | 2                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Very low         |
| PLA:VAL    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Very low         |
| ASE:LAM    | 0                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Very low         |
| ASE:LIT    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| ASE:OLA    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| ASE:PAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| ASE:QUE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| ASE:VAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| LAM:OLA    | 0                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Very low         |
| LAM:PAL    | 0                | Some concerns     | Suspected      | No concerns  | No concerns    | Major concerns | No concerns   | Very low         |
| LAM:QUE    | 0                | Some concerns     | Suspected      | No concerns  | No concerns    | Major concerns | No concerns   | Very low         |
| LAM:VAL    | 0                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Very low         |
| LIT:PAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| OLA:PAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| OLA:PLA    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| OLA:QUE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| OLA:VAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| PAL:QUE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| PAL:VAL    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | No concerns   | Low              |
| QUE:VAL    | 0                | No concerns       | Suspected      | No concerns  | No concerns    | No concerns    | No concerns   | Moderate         |
1.17. Diarrhea (5 studies, 2770 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|       | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures |
|-------|-----------------|--------------------|----------------------|------------------------|
|       | Ratio of risk ratios | P value            |                      |                        |
| LAM   | 0.377 (0.190, 0.749) | 0.749 (0.290, 1.932) | 0.518 (0.220, 1.221) | 0.656 (0.321, 1.343) |
| 0.340 (0.165, 0.698) | LIT 1.988 (0.980, 4.033) | 1.374 (0.783, 2.411) | 1.742 (1.171, 2.592) |
| 2.284 (0.956, 5.459) | QUE 0.691 (0.295, 1.623) | 0.877 (0.445, 1.726) |                      |                        |
| 1.285 (0.700, 2.361) | VAL 1.167 (0.613, 2.223) | 1.268 (0.712, 2.257) |                      |                        |
| 0.763 (0.342, 1.701) | PLA | 0.814 (0.398, 1.665) | 1.167 (0.613, 2.223) |                        |

Evaluation of heterogeneity and inconsistency

| Between study variance (τ²) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|-----------------------------|--------------------------|---------------------------------------------------|
|                             |                          | Q       | df | p               |
| 0.073                       | Moderate                 | 5.667   | 3  | 0.129           |

Inconsistency

|                  | NMA, RR (95%CI) | Direct, RR (95%CI) | Indirect, RR (95%CI) | Inconsistency measures |
|------------------|-----------------|--------------------|----------------------|------------------------|
|                  | Ratio of risk ratios | P value        |                      |                        |
| LAM vs LIT       | 0.340 (0.165, 0.698) | 0.340 (0.165, 0.698) | 1.042 (0.109, 9.959) | 0.326 (0.030, 3.483) | 0.353 |
| LAM vs PLA       | 0.656 (0.321, 1.343) | 0.763 (0.342, 1.701) | 0.362 (0.073, 1.783) | 2.107 (0.354, 12.557) | 0.413 |
| LIT vs QUE       | 1.988 (0.980, 4.033) | 2.284 (0.956, 5.459) | 1.517 (0.451, 5.103) | 1.506 (0.338, 6.706) | 0.591 |
| LIT vs VAL       | 1.374 (0.783, 2.411) | 1.285 (0.700, 2.361) | 2.035 (0.466, 8.884) | 0.632 (0.128, 3.111) | 0.572 |
| LIT vs PLA       | 1.742 (1.171, 2.592) | 1.663 (1.113, 2.485) | 14.209 (0.949, 212.725) | 0.117 (0.008, 1.805) | 0.124 |
| QUE vs PLA       | 0.877 (0.445, 1.726) | 0.814 (0.398, 1.665) | 1.664 (0.203, 13.614) | 0.489 (0.053, 4.502) | 0.527 |
| VAL vs PLA       | 1.268 (0.712, 2.257) | 1.167 (0.613, 2.223) | 1.770 (0.485, 6.451) | 0.659 (0.155, 2.797) | 0.572 |
### Rank probabilities

|     | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 |
|-----|--------|--------|--------|--------|--------|
| LAM | 0.690  | 0.212  | 0.062  | 0.031  | 0.006  |
| LIT | 0.001  | 0.007  | 0.028  | 0.186  | 0.779  |
| QUE | 0.235  | 0.442  | 0.177  | 0.106  | 0.040  |
| VAL | 0.045  | 0.109  | 0.179  | 0.506  | 0.162  |
| PLA | 0.029  | 0.231  | 0.555  | 0.171  | 0.014  |

### SUCRA

|     |      |
|-----|------|
| LAM | 0.86 |
| QUE | 0.62 |
| PLA | 0.58 |
| VAL | 0.38 |
| LIT | 0.07 |

### Comparison-adjusted funnel plot of studies of drugs versus placebo
## CINeMA rating

| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|------------------|------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| LAM:LIT    | 2                | Some concerns    | Suspected      | No concerns  | No concerns  | Major concerns | No concerns  | Very low          |
| LAM:PLA    | 2                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns  | No concerns  | Very low          |
| LIT:PLA    | 4                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns  | No concerns  | Very low          |
| LIT:QUE    | 1                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns  | No concerns  | Very low          |
| LIT:VAL    | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns  | No concerns  | Low              |
| PLA:QUE    | 2                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns  | No concerns  | Very low          |
| PLA:VAL    | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns  | No concerns  | Low              |
| LAM:QUE    | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns  | No concerns  | Very low          |
| LAM:VAL    | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns  | No concerns  | Very low          |
| QUE:VAL    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns  | No concerns  | Low              |
Supplementary Appendix 2. Two-dimensional plot of the result

Supplementary Appendix 2.1. Risk ratios of each drug for recurrence/relapse rate of any mood episode and for all-cause discontinuation compared to placebo

RR < 1 favors intervention
Supplementary Appendix 2.2. Risk ratios of each drug for recurrence/relapse rate of any mood episode and for discontinuation due to adverse event compared to placebo

RR < 1 favors intervention
Supplementary Appendix 2.3. Risk ratios of each drug for recurrence/relapse rate of depressive episodes and for recurrence/relapse rate of manic/hypomanic/mixed episodes compared to placebo

RR < 1 favors intervention
Supplementary Appendix 3. Results of second network meta-analysis

3.1. Recurrence/relapse rate of any mood episodes (5 studies, 2399 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

| Treatment | Pairwise | NMA         | p-value | p-value |
|-----------|----------|-------------|---------|---------|
| ARI       | 1.482 (0.908, 2.417) | 0.633 (0.307, 1.303) | 1.553 (0.998, 2.417) | 0.981 (0.538, 1.789) | **0.595 (0.396, 0.894)** |
| LUR       | **0.427 (0.221, 0.823)** | 1.048 (0.759, 1.448) | 0.662 (0.394, 1.113) | **0.402 (0.306, 0.528)** |
| OLA       | **2.456 (1.318, 4.575)** | 1.551 (0.737, 3.261) | 0.941 (0.518, 1.710) |
| QUE       | 0.631 (0.393, 1.016) | **0.383 (0.322, 0.456)** |
| ZIP       | 0.607 (0.390, 0.944) | **0.607 (0.390, 0.944)** |

**Evaluation of heterogeneity and inconsistency**

| Study Source | Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|--------------|---------------------------------|--------------------------|---------------------------------------------------|
|              | 0.0484                          | Low to moderate          | Not estimate                                      |

**Rank probabilities**

| Treatment | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 |
|-----------|--------|--------|--------|--------|--------|--------|
| ARI       | 0.072  | 0.120  | 0.310  | 0.332  | 0.110  | 0.056  |
| LUR       | 0.369  | 0.357  | 0.168  | 0.067  | 0.024  | 0.014  |
| OLA       | 0.025  | 0.039  | 0.089  | 0.161  | 0.325  | 0.361  |
| QUE       | 0.458  | 0.362  | 0.125  | 0.041  | 0.011  | 0.003  |
| ZIP       | 0.076  | 0.120  | 0.296  | 0.317  | 0.133  | 0.058  |
| PLA       | 0.000  | 0.001  | 0.013  | 0.081  | 0.398  | 0.507  |
### SUCRA

| Drug | SUCRA |
|------|-------|
| QUE  | 0.85  |
| LUR  | 0.82  |
| ZIP  | 0.49  |
| ARI  | 0.48  |
| OLA  | 0.23  |
| PLA  | 0.14  |

![Comparison-adjusted funnel plot of studies of drugs versus placebo](image-url)
| Comparison   | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|--------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| ARI:PLA      | 1                 | No concerns       | Suspected      | No concerns  | No concerns | Major concerns | Major concerns | Very low          |
| LUR:PLA      | 1                 | Some concerns     | Suspected      | No concerns  | No concerns | Major concerns | Major concerns | Very low          |
| OLA:PLA      | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| PLA:QUE      | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | Major concerns | Very low      |
| PLA:ZIP      | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | Major concerns | Very low      |
| ARI:LUR      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:OLA      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:QUE      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:ZIP      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LUR:OLA      | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | Major concerns | Very low      |
| LUR:QUE      | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LUR:ZIP      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| OLA:QUE      | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| OLA:ZIP      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| QUE:ZIP      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
### 3.2. Recurrence/relapse rate of depressive episodes (5 studies, 2399 patients)

#### League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|      | ARI          | LUR          | QUE          | ZIP          | PLA          |
|------|--------------|--------------|--------------|--------------|--------------|
| Mean | 2.582 (1.291, 5.160) | 2.054 (1.074, 3.930) | 0.874 (0.363, 2.102) | 0.777 (0.428, 1.410) |
| 95% CI | 2.054 (1.074, 3.930) | 0.874 (0.363, 2.102) | 0.777 (0.428, 1.410) |

#### Evaluation of heterogeneity and inconsistency

|       | Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|-------|----------------------------------|--------------------------|----------------------------------------------------|
|       | Q | df | p  |
| 0.1082 | Moderate | Not estimate |

#### Rank probabilities

|      | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 |
|------|--------|--------|--------|--------|--------|
| ARI  | 0.051  | 0.088  | 0.404  | 0.248  | 0.209  |
| LUR  | 0.652  | 0.244  | 0.069  | 0.024  | 0.012  |
| QUE  | 0.259  | 0.595  | 0.112  | 0.026  | 0.009  |
| ZIP  | 0.038  | 0.068  | 0.302  | 0.290  | 0.303  |
| PLA  | 0.000  | 0.006  | 0.113  | 0.413  | 0.468  |
|   | SUCRA  |
|---|---------|
| LUR | 0.90    |
| QUE | 0.75    |
| ARI | 0.37    |
| ZIP | 0.29    |
| PLA | 0.19    |

Comparison-adjusted funnel plot of studies of drugs versus placebo
**CINeMA rating**

| Comparison  | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|-------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|-------------------|
| ARI:PLA     | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LUR:PLA     | 1                 | Some concerns     | Suspected      | No concerns  | No concerns  | Major concerns | Major concerns | Very low          |
| PLA:QUE     | 2                 | Some concerns     | Suspected      | No concerns  | No concerns  | Major concerns | Major concerns | Very low          |
| PLA:ZIP     | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| ARI:LUR     | 0                 | No concerns       | Suspected      | No concerns  | No concerns  | Major concerns | Major concerns | Very low          |
| ARI:QUE     | 0                 | No concerns       | Suspected      | No concerns  | No concerns  | Major concerns | Major concerns | Very low          |
| ARI:ZIP     | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LUR:QUE     | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low          |
| LUR:ZIP     | 0                 | No concerns       | Suspected      | No concerns  | No concerns  | Major concerns | Major concerns | Very low          |
| QUE:ZIP     | 0                 | No concerns       | Suspected      | No concerns  | No concerns  | Major concerns | Major concerns | Very low          |
3.3. Recurrence/relapse rate of manic/hypomanic/mixed episodes (5 studies, 2399 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half. The boldface result indicates statistical significance.

| ARI         | 0.588 (0.219, 1.583) | 0.821 (0.363, 1.857) | 0.724 (0.227, 2.310) | **0.322 (0.149, 0.693)** |
|------------|----------------------|----------------------|----------------------|--------------------------|
| LUR        | 1.395 (0.703, 2.769) | 1.230 (0.421, 3.595) | 0.547 (0.293, 1.023) |
| QUE        | 0.882 (0.353, 2.201) |
| ZIP        |                      |
|            | 0.322 (0.149, 0.693) | **0.392 (0.296, 0.519)** |
|            | 0.547 (0.293, 1.023) | 0.392 (0.296, 0.519) |
|            | 0.445 (0.186, 1.063) | PLA                  |

Evaluation of heterogeneity and inconsistency

| Between study variance (τ²) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|-----------------------------|--------------------------|-----------------------------------------------------|
| 0.9797                      | Moderate                 | Not estimate                                        |

Rank probabilities

|            | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 |
|------------|--------|--------|--------|--------|--------|
| ARI        | 0.468  | 0.244  | 0.166  | 0.101  | 0.021  |
| LUR        | 0.107  | 0.143  | 0.258  | 0.401  | 0.092  |
| QUE        | 0.172  | 0.378  | 0.321  | 0.122  | 0.008  |
| ZIP        | 0.253  | 0.234  | 0.229  | 0.223  | 0.061  |
| PLA        | 0.000  | 0.003  | 0.027  | 0.153  | 0.817  |
SUCRA

|   |   |
|---|---|
|ARI | 0.75 |
|QUE | 0.69 |
|ZIP | 0.56 |
|LUR | 0.43 |
|PLA | 0.06 |

Comparison-adjusted funnel plot of studies of drugs versus placebo
| Comparison   | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|--------------|------------------|------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| ARI:PLA      | 1                | No concerns      | Suspected      | No concerns  | No concerns | Major concerns| Major concerns| Very low         |
| LUR:PLA      | 1                | Some concerns    | Suspected      | No concerns  | Major concerns| No concerns  | Major concerns | Very low         |
| PLA:QUE      | 2                | Some concerns    | Suspected      | No concerns  | No concerns  | Major concerns| Major concerns| Very low         |
| PLA:ZIP      | 1                | No concerns      | Suspected      | No concerns  | Major concerns| No concerns  | Major concerns | Very low         |
| ARI:LUR      | 0                | No concerns      | Suspected      | No concerns  | Major concerns| No concerns  | Major concerns | Very low         |
| ARI:QUE      | 0                | No concerns      | Suspected      | No concerns  | Major concerns| No concerns  | Major concerns | Very low         |
| ARI:ZIP      | 0                | No concerns      | Suspected      | No concerns  | Major concerns| No concerns  | Major concerns | Very low         |
| LUR:QUE      | 0                | Some concerns    | Suspected      | No concerns  | Major concerns| No concerns  | Major concerns | Very low         |
| LUR:ZIP      | 0                | No concerns      | Suspected      | No concerns  | Major concerns| No concerns  | Major concerns | Very low         |
| QUE:ZIP      | 0                | No concerns      | Suspected      | No concerns  | Major concerns| No concerns  | Major concerns | Very low         |
3.4. All-cause discontinuation (6 studies, 2398 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|    | ARI    | LUR    | OLA    | QUE    | ZIP    | PLA    |
|----|--------|--------|--------|--------|--------|--------|
|    | 1.675 (0.804, 3.492) | 1.067 (0.512, 2.221) | 1.184 (0.631, 2.218) | 1.239 (0.577, 2.663) | 0.817 (0.483, 1.384) |
|    | 1.067 (0.309, 1.311) | 0.706 (0.382, 1.307) | 0.739 (0.348, 1.572) | 0.488 (0.293, 0.813) |
|    | 1.109 (0.600, 2.050) | 1.161 (0.547, 2.467) | 0.766 (0.460, 1.276) | 0.691 (0.491, 0.972) |
|    | 0.766 (0.460, 1.276) | 0.691 (0.491, 0.972) | 0.660 (0.379, 1.149) | PLA    |

Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|---------------------------------|--------------------------|-----------------------------------------------------|
| 0.1310                          | High                     | Not estimate                                        |

Rank probabilities

|    | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 |
|----|--------|--------|--------|--------|--------|--------|
| ARI| 0.076  | 0.134  | 0.163  | 0.198  | 0.210  | 0.220  |
| LUR| 0.557  | 0.204  | 0.115  | 0.065  | 0.036  | 0.025  |
| OLA| 0.098  | 0.160  | 0.186  | 0.209  | 0.181  | 0.166  |
| QUE| 0.081  | 0.241  | 0.291  | 0.230  | 0.112  | 0.046  |
| ZIP| 0.188  | 0.258  | 0.210  | 0.147  | 0.104  | 0.093  |
| PLA| 0.000  | 0.003  | 0.036  | 0.152  | 0.358  | 0.451  |
### SUCRA Comparison

| Drug | SUCRA Value |
|------|-------------|
| LUR  | 0.80        |
| OLA  | 0.76        |
| QUE  | 0.58        |
| ZIP  | 0.47        |
| ARI  | 0.30        |
| PLA  | 0.09        |

![Comparison-adjusted funnel plot of studies of drugs versus placebo](image-url)
| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|------------------|------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| ARI:PLA    | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| LUR:PLA    | 1                | Some concerns    | Suspected      | No concerns  | No concerns    | Major concerns | Major concerns | Very low         |
| OLA:PLA    | 1                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| PLA:QUE    | 2                | Some concerns    | Suspected      | No concerns  | No concerns    | Major concerns | Major concerns | Very low         |
| PLA:ZIP    | 1                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI:LUR    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI:OLA    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI:QUE    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| ARI:ZIP    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| LUR:OLA    | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| LUR:QUE    | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| LUR:ZIP    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| OLA:QUE    | 0                | Some concerns    | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| OLA:ZIP    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| QUE:ZIP    | 0                | No concerns      | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
3.5. Discontinuation due to adverse event (6 studies, 2398 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|       | ARI      | LUR      | OLA      | QUE      | ZIP      | PLA      |
|-------|----------|----------|----------|----------|----------|----------|
|       | 1.306 (0.065, 26.177) | 2.166 (0.110, 42.598) | 0.599 (0.049, 7.363) | 1.953 (0.109, 34.949) | 1.274 (0.168, 9.644) |
|       | LUR      | 1.658 (0.074, 37.159) | 0.458 (0.032, 6.573) | 1.495 (0.073, 30.615) | 0.976 (0.107, 8.908) |
|       | OLA      | 0.276 (0.020, 3.879) | 0.901 (0.045, 18.112) | 0.588 (0.066, 5.233)  |
|       | QUE      | 3.262 (0.259, 41.161) | 2.129 (0.483, 9.386) | 0.652 (0.084, 5.096)  |
| 1.274 (0.168, 9.644) | 0.976 (0.107, 8.908) | 0.588 (0.066, 5.233) | 2.129 (0.483, 9.386) | 0.652 (0.084, 5.096) | PLA |

Evaluation of heterogeneity and inconsistency

| Between study variance (τ²) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|---------------------------|--------------------------|---------------------------------------------------|
| 0.81                      | High                     | Not estimate                                      |

Rank probabilities

|       | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 |
|-------|--------|--------|--------|--------|--------|--------|
| ARI   | 0.093  | 0.137  | 0.152  | 0.165  | 0.237  | 0.216  |
| LUR   | 0.197  | 0.208  | 0.158  | 0.137  | 0.152  | 0.148  |
| OLA   | 0.384  | 0.234  | 0.141  | 0.090  | 0.088  | 0.064  |
| QUE   | 0.018  | 0.043  | 0.075  | 0.129  | 0.261  | 0.476  |
| ZIP   | 0.295  | 0.264  | 0.157  | 0.106  | 0.102  | 0.077  |
| PLA   | 0.013  | 0.115  | 0.318  | 0.373  | 0.161  | 0.020  |
### SUCRA

| Drug | SUCRA |
|------|-------|
| OLA  | 0.71  |
| ZIP  | 0.68  |
| PLA  | 0.51  |
| LUR  | 0.50  |
| ARI  | 0.41  |
| QUE  | 0.19  |

**Comparison-adjusted funnel plot of studies of drugs versus placebo**
## CINEMA rating

| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|------------------|-------------------|----------------|--------------|-------------|---------------|--------------|------------------|
| ARI:PLA    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| LUR:PLA    | 1                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| OLA:PLA    | 1                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| PLA:QUE    | 2                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| PLA:ZIP    | 1                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| ARI:LUR    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| ARI:OLA    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| ARI:QUE    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| ARIZIP     | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| LUR:OLA    | 0                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| LUR:QUE    | 0                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| LUR:ZIP    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| OLA:QUE    | 0                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| OLA:ZIP    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
| QUE:ZIP    | 0                | No concerns       | Suspected      | No concerns  | Major concerns | No concerns  | Major concerns | Very low         |
## Supplementary Appendix 2.6. Mortality

| Intervention | n | Total patients | Intervention | n | Total patients |
|--------------|---|----------------|--------------|---|----------------|
| Bowden 2010  | ZIP+LIT/VAL | 0 | 127 | LIT/VAL | 0 | 112 |
| Calabrese 2017 | LUR+LIT/VAL | 0 | 246 | LIT/VAL | 0 | 150 |
| Marcus 2011 | ARI+LIT/VAL | 1 | 168 | LIT/VAL | 1 | 169 |
| Suppes 2009 | QUE+LIT/VAL | 1 | 310 | LIT/VAL | 0 | 313 |
| Tohen 2004 | OLA+LIT/VAL |  |  | LIT/VAL |  |  |
| Vieta 2008 | QUE+LIT/VAL | 1 | 336 | LIT/VAL | 3 | 367 |

## Supplementary Appendix 2.7. Completed suicide

| Intervention | n | Total patients | Intervention | n | Total patients |
|--------------|---|----------------|--------------|---|----------------|
| Bowden 2010  | ZIP+LIT/VAL | 0 | 127 | LIT/VAL | 0 | 112 |
| Calabrese 2017 | LUR+LIT/VAL | 0 | 246 | LIT/VAL | 0 | 150 |
| Marcus 2011 | ARI+LIT/VAL | 1 | 168 | LIT/VAL | 0 | 169 |
| Suppes 2009 | QUE+LIT/VAL | 1 | 310 | LIT/VAL | 0 | 313 |
| Tohen 2004 | OLA+LIT/VAL |  |  | LIT/VAL |  |  |
| Vieta 2008 | QUE+LIT/VAL | 1 | 336 | LIT/VAL | 1 | 367 |
3.8. Extrapyramidal symptoms (6 studies, 2398 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

| ARI    | 1.732 (0.464, 6.465) | 1.527 (0.300, 7.783) | 2.362 (0.704, 7.915) | 1.426 (0.278, 7.318) | 2.515 (0.805, 7.861) |
|--------|----------------------|----------------------|----------------------|----------------------|----------------------|
| LUR    | 0.881 (0.231, 3.359) | 1.363 (0.628, 2.957) | 0.823 (0.214, 3.162) | 1.452 (0.750, 2.809) |                      |
| OL A   | 1.547 (0.451, 5.302) | 0.934 (0.179, 4.873) | 1.647 (0.515, 5.272) |                      |                      |
| QUE    |                      | 0.604 (0.175, 2.089) | 1.065 (0.710, 1.597) |                      |                      |
| ZIP    | 1.764 (0.546, 5.700) |                      |                      |                      |                      |
| PLA    |                      |                      |                      |                      |                      |

2.515 (0.805, 7.861)   1.452 (0.750, 2.809)   1.647 (0.515, 5.272)   1.065 (0.710, 1.597)   1.764 (0.546, 5.700)   PLA

Evaluation of heterogeneity and inconsistency

| Between study variance (τ²) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|-----------------------------|--------------------------|-----------------------------------------------------|
|                             | Q                        | df        | p         |
| 0.0961                      | Moderate                 | Not estimate |

Rank probabilities

|          | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 |
|----------|--------|--------|--------|--------|--------|--------|
| ARI      | 0.063  | 0.060  | 0.072  | 0.129  | 0.241  | 0.434  |
| LUR      | 0.122  | 0.114  | 0.162  | 0.238  | 0.235  | 0.130  |
| OLA      | 0.218  | 0.104  | 0.115  | 0.173  | 0.206  | 0.184  |
| QUE      | 0.250  | 0.248  | 0.221  | 0.171  | 0.086  | 0.024  |
| ZIP      | 0.180  | 0.095  | 0.126  | 0.164  | 0.209  | 0.226  |
| PLA      | 0.167  | 0.379  | 0.304  | 0.126  | 0.023  | 0.002  |
SUCRA

|   |   |
|---|---|
| PLA | 0.78 |
| QUE | 0.70 |
| LUR | 0.49 |
| OLA | 0.41 |
| ZIP | 0.40 |
| ARI | 0.23 |
### CINeMA rating

| Comparison   | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|--------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|-------------------|
| ARI:PLA      | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| LUR:PLA      | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| OLA:PLA      | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| PLA:QUE      | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| PLA:ZIP      | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| ARI:LUR      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| ARI:OLA      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| ARI:QUE      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| ARI:ZIP      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| LUR:OLA      | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| LUR:QUE      | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| OLA:QUE      | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| OLA:ZIP      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
| QUE:ZIP      | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns    | Major concerns | Very low          |
3.9. Somnolence (3 studies, 1425 patients)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half. The boldface result indicates statistical significance.

|       | OLA          | QUE          | PLA          |
|-------|--------------|--------------|--------------|
|       | 0.591 (0.097, 3.611) | 3.983 (1.450, 10.943) | 2.353 (0.524, 10.568) |
|       | 2.353 (0.524, 10.568) | 3.983 (1.450, 10.943) |               |

Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|---------------------------------------------------|
| 0.8910                           | High                     | Not estimate                                      |

Rank probabilities

|       | Rank 1 | Rank 2 | Rank 3 |
|-------|--------|--------|--------|
| OLA   | 0.218  | 0.482  | 0.300  |
| QUE   | 0.036  | 0.278  | 0.686  |
| PLA   | 0.747  | 0.240  | 0.014  |
SUCRA

|     |     |
|-----|-----|
| PLA | 0.90|
| OLA | 0.41|
| QUE | 0.19|

Comparison-adjusted funnel plot of studies of drugs versus placebo
| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| OLA:PLA    | 1                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
| PLA:QUE    | 2                | Some concerns     | Suspected      | No concerns  | No concerns   | Major concerns | Major concerns | Very low         |
| OLA:QUE    | 0                | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns   | Major concerns | Very low         |
### 3.10. Insomnia (6 studies, 2398 patients)

#### League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half. The boldface result indicates statistical significance.

|   | ARI       | LUR       | OLA       | QUE       | ZIP       | PLA       |
|---|-----------|-----------|-----------|-----------|-----------|-----------|
|   | 0.990 (0.244, 4.016) | 3.908 (0.621, 24.611) | 1.501 (0.486, 4.636) | 1.100 (0.256, 4.733) | 0.566 (0.211, 1.518) |
| LUR | 3.948 (0.624, 24.963) | 1.516 (0.487, 4.714) | 1.111 (0.257, 4.806) | 0.572 (0.212, 1.544) |
| OLA | 0.384 (0.074, 1.993) | 0.281 (0.043, 1.862) | **0.145 (0.031, 0.684)** | |
| QUE | 0.733 (0.219, 2.450) | **0.377 (0.218, 0.652)** | |
| ZIP | 0.572 (0.212, 1.544) | 0.514 (0.176, 1.508) | **0.145 (0.031, 0.684)** |

#### Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|---------------------------------|--------------------------|---------------------------------------------------|
| 0.4264                          | High                     | Not estimate                                      |

#### Rank probabilities

|     | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 |
|-----|--------|--------|--------|--------|--------|--------|
| ARI | 0.059  | 0.173  | 0.186  | 0.226  | 0.204  | 0.152  |
| LUR | 0.064  | 0.164  | 0.197  | 0.217  | 0.206  | 0.152  |
| OLA | 0.711  | 0.136  | 0.073  | 0.041  | 0.022  | 0.018  |
| QUE | 0.078  | 0.309  | 0.319  | 0.192  | 0.080  | 0.024  |
| ZIP | 0.089  | 0.216  | 0.201  | 0.197  | 0.173  | 0.124  |
| PLA | 0.000  | 0.003  | 0.024  | 0.127  | 0.316  | 0.530  |
SUCRA

| Drug | SUCRA |
|------|-------|
| OLA  | 0.89  |
| QUE  | 0.63  |
| ZIP  | 0.48  |
| ARI  | 0.43  |
| LUR  | 0.42  |
| PLA  | 0.15  |
## CINeMA rating

| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|------------------|-------------------|----------------|---------------|-------------|---------------|-------------|------------------|
| ARI:PLA    | 1                | No concerns       | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| LUR:PLA    | 1                | Some concerns     | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| OLA:PLA    | 1                | Some concerns     | Suspected      | No concerns   | Major concerns | Major concerns | Major concerns | Very low         |
| PLA:QUE    | 2                | Some concerns     | Suspected      | No concerns   | Major concerns | Major concerns | Major concerns | Very low         |
| PLA:ZIP    | 1                | No concerns       | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| ARI:LUR    | 0                | No concerns       | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| ARI:OLA    | 0                | No concerns       | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| ARI:QUE    | 0                | No concerns       | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| ARI:ZIP    | 0                | No concerns       | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| LUR:OLA    | 0                | Some concerns     | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| LUR:QUE    | 0                | Some concerns     | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| LUR:ZIP    | 0                | No concerns       | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| OLA:QUE    | 0                | Some concerns     | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| OLA:ZIP    | 0                | No concerns       | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
| QUE:ZIP    | 0                | No concerns       | Suspected      | No concerns   | Major concerns | No concerns   | Major concerns | Very low         |
3.11. Increased weight (6 studies)

League table

Results from pairwise meta-analysis are presented in the left lower half and results from network meta-analysis in the upper right half.

The boldface result indicates statistical significance.

|        | ARI       | LUR       | OLA       | QUE       | ZIP       | PLA       |
|--------|-----------|-----------|-----------|-----------|-----------|-----------|
| Mean   | 0.569 (0.225, 1.438) | 0.463 (0.115, 1.866) | 1.320 (0.365, 4.773) | 3.234 (1.000, 10.457) | 1.029 (0.356, 2.971) | 0.204 (0.455, 0.275) |
|       | 0.263 (0.071, 0.975) | 0.611 (0.250, 1.492) | 4.269 (0.872, 20.907) | 3.327 (2.013, 5.501) | 4.392 (1.346, 14.336) |
|       | 0.348 (0.164, 0.738) | 1.975 (0.543, 7.192) | 4.392 (1.346, 14.336) | 1.157 (0.661, 2.025) | 1.157 (0.661, 2.025) |
|        | 1.124 (0.339, 3.730) | 2.033 (0.971, 4.253) | 1.029 (0.356, 2.971) | 1.029 (0.356, 2.971) | 1.029 (0.356, 2.971) |

Evaluation of heterogeneity and inconsistency

| Between study variance ($\tau^2$) | Heterogeneity assessment | Random-effects design-by-treatment interaction model |
|----------------------------------|--------------------------|----------------------------------------------------|
| 0.1998                           | High                     | Not estimate                                       |

Rank probabilities

|        | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 |
|--------|--------|--------|--------|--------|--------|--------|
| ARI    | 0.252  | 0.233  | 0.276  | 0.148  | 0.064  | 0.028  |
| LUR    | 0.073  | 0.094  | 0.156  | 0.363  | 0.209  | 0.105  |
| OLA    | 0.021  | 0.031  | 0.059  | 0.141  | 0.245  | 0.503  |
| QUE    | 0.004  | 0.017  | 0.051  | 0.171  | 0.420  | 0.337  |
| ZIP    | 0.446  | 0.170  | 0.184  | 0.117  | 0.056  | 0.028  |
| PLA    | 0.204  | 0.455  | 0.275  | 0.060  | 0.006  | 0.000  |
Comparison-adjusted funnel plot of studies of drugs versus placebo

|   | SUCRA   |
|---|---------|
| PLA| 0.79    |
| ZIP| 0.72    |
| ARI| 0.68    |
| LUR| 0.44    |
| QUE| 0.23    |
| OLA| 0.13    |

Effect centered at comparison-specific pooled effect.
| Comparison     | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|---------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| ARI:PLA       | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| LUR:PLA       | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| OLA:PLA       | 1                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| PLA:QUE       | 2                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| PLA:ZIP       | 1                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| ARI:LUR       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| ARI:OLA       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| ARI:QUE       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| ARI:ZIP       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| LUR:OLA       | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| LUR:QUE       | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| LUR:ZIP       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| OLA:QUE       | 0                 | Some concerns     | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| OLA:ZIP       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |
| QUE:ZIP       | 0                 | No concerns       | Suspected      | No concerns  | Major concerns | No concerns     | Major concerns | Very low          |