Supplementary Table 1 Characteristics of included randomized, double-blind, placebo-controlled trials in the acute treatment of pediatric patients with bipolar disorder

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Research Area** | **Age years** | **Duration weeks** | **Diagnosis** | | **Titration** | |
| **Lithium** |  |  |  |  | |  | |
| Findling RL, et al. (2015) [15] | North America | 7-17 | 8 | BDI, manic or mixed episode | | Participants weighing ＜ 30 kg started with 600 mg/d; all other participants began lithium therapy with 900 mg/d. Dose increases of 300 mg/d could occur at study visits and via telephone call during the middle of the first week of randomized treatment based on patients’ situation. | |
| **Divalproex** |  |  |  |  | |  | |
| Wagner KD, et al. (2009) [16] | North America | 7-17 | 4 | BDI, manic or mixed episode | | Divalproex drug was initiated at 15 mg/kg per day (not to exceed 750 mg) and titrated in 250-mg increments every 1 to 3 days to clinical response and/or a serum valproate concentration within the target range of 80 to 125 ug/mL, as deemed appropriate by the investigator, to a maximum dosage of 35 mg/kg per day. | |
| **Oxcarbazepine** |  |  |  |  | |  | |
| Wagner KD, et al. (2006) [17] | North America | 7-18 | 7 | BDI, manic or mixed episode | | The oxcarbazepine dose was titrated upward by 300 mg every 2 days to a maximum dose level of 900–2400 mg/d based on body weight or to the maximum dose tolerated. At the investigator’s discretion, the dose could be tapered downward by 300 mg/d if the patient experienced intolerable adverse effects. | |
| **Aripiprazole** |  |  |  |  | |  | |
| Findling RL, et al. (2009) [18] | North America | 10-17 | 4 | BDI, manic or mixed episode | | Aripiprazole dosing started with 2 mg/d (days 1 and 2), 5 mg/d (days 3 and 4), and 10 mg/d on day 5. Subjects in the 10 mg group remained at that target dose, and titration continued for the 30 mg group with 10 mg/d (days 5 and 6), 15 mg/d (days 7 and 8), 20 mg/d (days 9 and 10), and 25 mg/d (days 11 and 12) and concluded with the target dose of 30 mg/d on day 13. | |
| **Asenapine** |  |  |  |  | |  | |
| Findling RL, et al. (2015) [19] | Europe, North America | 10-17 | 4 | BDI, manic or mixed episode | | Patients were randomized to asenapine: 2.5 mg BID from day 1; 5 mg BID administered as 2.5 mg BID for 3 days, then 5 mg BID thereafter; and 10 mg BID administered as 2.5 mg BID for 3 days, then 5 mg BID for 3 days, then 10 mg BID | |
| **Olanzapine** |  |  |  |  | |  | |
| Tohen M, et al. (2007) [20] | North America | 13-17 | 3 | manic or mixed episode | | Patients in the olanzapine group received a starting dosage of 2.5 mg/d or 5.0 mg/d, which could subsequently be increased by 2.5 mg/d or 5.0 mg/d increments at the investigator’s discretion. | |
| **Quetiapine** |  |  |  |  | |  | |
| Pathak S, et al. (2013) [21] | North America | 10-17 | 3 | BD, manic episode | | The quetiapine dose was titrated from 50 mg/d on day 1 to 100 mg/d on day 2 and increased by 100 mg each day to 400 mg/d by day 5 or 600 mg/d by day 7. | |
| **Risperidone** |  |  |  |  | |  | |
| Haas M, et al. (2009) [22] | North America | 10-17 | 3 | BDI, manic or mixed episode | | The initial dose was 0.25 mg/d, and doses were increased by increments of 0.25 to 1 mg/d once every 1–2 days. Doses were titrated to the minimum dose within the assigned target ranges by day 7 of treatment. Investigators were instructed to continuously increase the dose daily from days 8 through 10 until the maximum tolerated dose within the assigned range was achieved. After day 10, subjects were maintained at that dose for the remainder of the study; further dose adjustments were allowed only for tolerability reasons but were required to be within the assigned target range. | |
| **Ziprasidone** |  |  |  |  | |  | |
| Findling RL, et al. (2013) [23] | North America | 10-17 | 4 | BDI, manic or mixed episode | | Ziprasidone was administered as oral capsules twice daily with meals and titrated over a 1–2-week period from a starting dose of 20 mg/day (beginning with an evening dose) with 20 mg/day dose increases every second day up to a target dose of 120–160 mg/day for subjects weighing ＞ 45 kg by day 14, and up to 60–80 mg/day for subjects weighing < 45 kg. For subjects requiring a more rapid onset of action based on their clinical history and symptoms, daily dose increases of 20 mg/day were permitted. | |
| **Lurasidone** |  |  |  |  | |  | |
| DelBello MP, et al. (2017) [24] | Asia, Europe, North and South America | 10-17 | 6 | BDI, depressive episode | | Treatment with lurasidone was initiated at a daily dose of lurasidone 20 mg for 7 days, with flexible dosing, in the range of 20-80 mg/day permitted after 7 days. | |
| **Olanzapine-fluoxetine combination** | |  |  | |  | |  |
| Detke HC, et al. (2015) [25] | Europe, North and South America | 10-17 | 8 | | BDI, depressive episode | | Patients randomized to OFC were initiated at a dose of 3/25 mg, which was increased to 6/25 mg at day 3, 6/50 mg at week 1, and 12/50 mg at week 2, with flexible dosing thereafter among the allowed doses of 6/25, 6/50, 12/25, and 12/50 mg. |
| **Quetiapine** |  |  |  |  | |  | |
| Findling RL, et al. (2014) [26] | Asia, Europe, North and South America, South Africa | 10-17 | 8 | BDI or II, depressive episode | | Doses of quetiapine-XR were titrated in 50 mg increments, starting at 50 mg on day 1, 100 mg on day 2, and 150 mg on day 3. | |

Abbreviations: BD: bipolar disorder; BDI: bipolar I disorder; BDII: bipolar II disorder; BID: twice daily; ER or XR: extended-release; OFC: olanzapine/fluoxetine combination.

Supplementary Table 2 Characteristics of included randomized, double-blind, placebo-controlled trials in the acute treatment of adult patients with bipolar disorder

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Research Area** | **Age years** | **Duration weeks** | **Diagnosis** | **Titration** |
| **Lithium** |  |  |  |  |  |
| Keck PE, et al (2009) [27] | North America | ≥ 18 | 3 | BDI, acute manic or mixed episode | Initial dose was 900 mg/d divided over three doses. The dose could be increased to 1200 mg/d at day 4 and up to 1500 mg/d at day 7. Lithium doses could be altered based on lithium serum concentrations. |
| Bowden CL, et al (2005) [28] | Asia, Europe | ≥ 18 | 12 | BDI, acute manic or mixed episode | Initial dose was 900 mg/d. Dose adjustment between 5 and 84 was at the investigator’s discretion in order to optimize efficacy and tolerability. |
| **Divalproex** |  |  |  |  |  |
| Hirschfeld RM, et al. (2010) [29] | North America | 18-65 | 3 | BDI, manic or mixed episode | Initial dose was 20mg/kg/d, with titration allowed at the investigator’s discretion on study days 5,15,20. |
| Tohen M, et al. (2008) [30] | Europe, North America | 18-65 | 3 | BDI, manic or mixed episode | Divalproex (500–2500 mg) was administered orally BID (for the 500 mg) or 3 times daily (for the 750 mg to 2500 mg) |
| Bowden CL, et al. (2006) [31] | North America | 18-65 | 3 | BDI, manic or mixed episode | Initial dose was 25mg/kg/d. On day 3, all patients had the daily dose increased by an additional 500mg. Additional dose adjustment could occur on days 7, 12, 17 at the investigator’s discretion based on clinical effect, adverse events, and serum valproate concentration. |
| Bowden CL, et al. (1994) [32] | North America | 18-65 | 3 | manic episode | Divalproex sodium was administered at an initial dose of 750 mg/d. On day 3, the total daily dosages of divalproex were increased to 1000 mg. Thereafter, medication adjustments were made on days 7, 10, 12, 14, and 17. |
| **Aripiprazole** |  |  |  |  |  |
| Kanba S, et al. (2014) [33] | Asia | 18-64 | 3 | BDI, manic or mixed episode | Aripiprazole was started at a dose of 24 mg/d, but the dose could be reduced to 12 mg/d for tolerability, if needed, based on the judgment of the investigator. |
| El Mallakh RS, et al. (2010) [34] | North and South America | ≥ 18 | 3 | BDI, manic or mixed episode | Initial fixed doses were 15 or 30 mg/d. Aripiprazole was given as fixed doses from the first day of treatment; dose modifications were not allowed during the double-blind phase of the study. |
| Young AH, et al. (2009) [35] | Europe, North and South America, South Africa | ≥ 18 | 3 | BDI, manic or mixed episode | Patients started aripiprazole at 15 mg/d. At day 4, investigators could increase the aripiprazole to 30 mg/d. Doses could be adjusted throughout the study based on tolerability and clinical response. |
| Keck PE, et al. (2009) [27] | North America | ≥ 18 | 3 | BDI, manic or mixed episode | Initial dose was 15 mg/d, orally, and QD; after day 4, the dose could be increased to 30 mg/d. Adjustments between aripiprazole 15 or 30 mg/d were made at any time during the study based on tolerability and clinical response. |
| Sachs G, et al. (2006) [36] | n/a | ≥ 18 | 3 | BDI, manic or mixed episode | Aripiprazole was started at a dose of 30 mg/d, but could be reduced to 15 mg/d for tolerability and subsequently increased to 30 mg/d for clinical response. |
| Keck PE Jr, et al. (2003) [37] | North America | ≥ 18 | 3 | BDI, manic or mixed episode | Initial aripiprazole was 30 mg/d. Aripiprazole dose could be reduced to 15mg/d for tolerability if needed. |
| **Asenapine** |  |  |  |  |  |
| Landbloom RL, et al. (2016) [38] | Europe, North America | ≥ 18 | 3 | BDI, manic or mixed episode | The asenapine 5 mg BID cohort received 5 mg BID every day, whereas patients in the asenapine 10 mg BID cohort received 5 mg BID on day 1 and 10 mg BID thereafter. |
| McIntyre RS, et al. (2010) [39] | Asia, Europe, North America | ≥ 18 | 3 | BDI, manic or mixed episode | Asenapine treatment was initiated at 10 mg BID on day 1 and was flexible (5 or 10 mg BID) thereafter. |
| McIntyre RS, et al. (2009) [40] | Asia, Europe, North America | ≥ 18 | 3 | BDI, manic or mixed episode | Asenapine treatment was initiated at 10 mg BID on day 1 and was flexible (5 or 10 mg BID) thereafter. |
| **Olanzapine** |  |  |  |  |  |
| Katagiri H, et al. (2012) [41] | Asia | 20-65 | 3 | BDI, manic or mixed episode | Olanzapine at an initial dose of 10 mg/d followed by a flexible dose (5 to 20 mg/d). |
| McIntyre RS, et al. (2010) [39] | Asia, Europe, North America | ≥ 18 | 3 | BDI, manic or mixed episode | Olanzapine treatment was initiated at 15 mg QD on day 1 and was flexible (5–20 mg QD) thereafter. |
| McIntyre RS, et al. (2009) [40] | Asia, Europe, North America | ≥ 18 | 3 | BDI, manic or mixed episode | Olanzapine treatment was initiated at 15 mg QD on day 1 and was flexible (5–20 mg QD) thereafter. |
| Tohen M, et al. (2008) [30] | Europe, North America | 18-65 | 3 | BDI, manic or mixed episode | Olanzapine (5–20 mg) was administered orally QD in the evening. |
| Tohen M, et al. (2000) [42] | North America | 18-70 | 3 | BD, manic or mixed episode | The starting dose of olanzapine was 15mg/d. After first day of therapy, the daily dose could be adjusted upward or downward, as clinical indicated, by 5-mg increments or decrements within the allowed dose range 5-20mg/d. |
| Tohen M, et al. (1999) [43] | North America | 18-65 | 3 | BD, manic or mixed episode | Patients began double-blind therapy with olanzapine, 10 mg (two 5-mg tablets) QD, preferably in the evening. After the first day of treatment, the daily dose could be adjusted upward or downward, as clinically indicated, by 5-mg increments/decrements within the allowed dosage range of 5–20 mg/d. Decreases in dosage because of adverse events could occur at any time by any number of one-tablet (5-mg) decrements (at the investigator’s discretion), to a minimum of one tablet per day. |
| **Quetiapine** |  |  |  |  |  |
| Vieta E, et al. (2010) [44] | Asia, Europe, North America | 18-65 | 3 | BDI, manic or mixed episode | Quetiapine was initiated at 100 mg/d on day 1, with forced titration to 400 mg/d at day 4, and subsequent dose adjustments in increments of 200 mg/d to a maximum of 800 mg/d, or decrements as deemed necessary by the investigator within the dose range of 400–800 mg/d. |
| McIntyre RS, et al (2005) [45] | Asia, Europe, South America | ≥ 18 | 12 | BDI, acute manic episode | Quetiapine was initiated at target doses of 100 mg/d on day 1, increasing by steps of 100 mg/d to 400 mg/d on day 4. To optimize efficacy and tolerability, the quetiapine dose could then be adjusted up to 600 mg/d on day 5 and up to 800 mg/d thereafter at the investigator’s discretion |
| Bowden CL, et al (2005) [28] | Asia, Europe | ≥ 18 | 12 | BDI, acute manic or mixed episode | Initial dose was 100mg on day 1, 200mg on day 2, 300mg on day 3, 400mg on day 4. Quetiapine could be adjusted up to 600mg/d on day 5 and 800mg/d thereafter. |
| **Risperidone** |  |  |  |  |  |
| Smulevic AB, et al. (2005) [46] | n/a | ≥ 18 | 3 | BDI, manic or mixed episode | Patients in the risperidone group received a single 2-mg dose on day 1 which could be increased or decreased by the investigator by 1 mg daily beginning on day 2 to a minimum of 1 mg/d or a maximum of 6 mg/d on day 5. |
| Khanna S, et al. (2005) [47] | Asia | ≥ 18 | 3 | BDI, manic or mixed episode | Patients were given a single 3mg dose on day 1. On day 2, at the discretion of the investigator, each patient’s once-daily dose (administered in the evening) could be reduced to 2mg or increased to 4mg. On day 3, the daily dose could be reduced to 1mg or increased to 5mg. On day 4 and thereafter the daily dose could be increased to 6mg. Throughout the trial, increases in risperidone dosage were made in increments of 1mg daily and the daily dose could be between 1mg and 6mg. |
| Hirschfeld RM, et al. (2004) [48] | North America | ≥ 18 | 3 | BDI, manic episode | Patients assigned to risperidone treatment received a single 3-mg dose of the study drug on day 1. The daily dose could be adjusted to 2-4 mg on day 2, to 1-5 mg on day 3, and to 1-6 mg on day 4 and thereafter at the discretion of the investigator. |
| **Ziprasidone** |  |  |  |  |  |
| Vieta E, et al. (2010) [49] | Asia, Europe, North America | ≥ 18 | 3 | BDI, manic episode | Ziprasidone were 80–160 mg/d (40, 60 or 80 mg BID). |
| Potkin SG, et al. (2005) [50] | North and South America | ≥ 18 | 3 | BDI, manic episode | Ziprasidone was initiated at 80 mg/d and could be adjusted by a maximum of 40 mg/d starting on day 2, within the range of 80 to 160 mg/d (40–80 mg BID) for the remainder of the trial. |
| Keck PE Jr, et al. (2003) [51] | North and South America | ＞18 | 3 | BDI, manic episode | Ziprasidone (given with meals) was started at 40 mg BID on day 1, increased to 80 mg BID on day 2, and adjusted by a maximum of 40 mg/d within the range of 80–160 mg/d during the course of the trial. |
| **Lurasidone** |  |  |  |  |  |
| Loebel A, et al. (2014) [52] | Asia, Europe, North America, South Africa | 18-75 | 6 | BDI, depressive episode | Patients assigned to receive lurasidone 20–60 mg/d were treated with 20 mg/d for days 1–7. Patients assigned to the lurasidone 80–120 mg/d arm received a fixed titration of lurasidone as follows: 20 mg/d for days 1–2, 40 mg/d for days 3–4, 60 mg/d for days 5–6 and 80 mg/d on day 7. In both treatment arms, lurasidone dosing adjustments within the assigned dosing range were permitted after 7 days to optimize efficacy and tolerability. |
| **Olanzapine/fluoxetine combination** | |  |  |  |  |
| Tohen M, et al. (2003) [53] | n/a | ≥ 18 | 8 | BDI, depressive episode | OFC therapy was initiated at 6 and 25 mg/d but could be administered at 6 and 50 or 12 and 50 mg/d after at least 1 day at each dose. |
| **Quetiapine** |  |  |  |  |  |
| Murasaki M, et al. (2018) [54] | Asia | 20-64 | 8 | BDI or II, depressive episode | Patients in the quetiapine XR 150 mg group were started on an initial dose of 50 mg/d and titrated to 150 mg/d on day 3. In the quetiapine XR 300 mg group, patients were started on an initial dose of 50 mg/d and titrated to 150 mg/d on day 3 and 300 mg/d on day 5. |
| Li H, et al. (2016) [55] | Asia | 18-65 | 8 | BDI or II, depressive episode | The quetiapine XR doses were titrated in 50-mg increments, starting at 50 mg on day 1 to 100 mg and 200 mg on days 2 and 3, and then to 300 mg from day 4 until day 56, respectively. |
| Suppes T, et al. (2010) [56] | North America | 18-65 | 8 | BDI or II, depressive episode | The quetiapine XR dose was titrated from 50 mg on Day 1 to 100 mg on day 2, 200 mg on day 3, and to a maximum of 300 mg on day 4. |

Abbreviations: BD: bipolar disorder; BDI: bipolar I disorder; BDII: bipolar II disorder; BID: twice daily; ER or XR: extended-release; OFC: olanzapine/fluoxetine combination; QD: once daily.

Supplementary Table 3 Single analysis of each randomized, double-blind, placebo-controlled trial for the risk of discontinuation due to adverse events, ≥ 7% weight gain, and somnolence in the acute treatment of pediatric patients with bipolar disorder

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Treatment Arm** | **Discontinuation Due to Adverse Events** | | | | **≥ 7% Weight Gain** | | | | **Self-Report Somnolence** | | | |
| **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** | **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** | **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** |
| **Bipolar Mania** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Findling RL, et al. (2015) [15] | Li < 1.4mEq/L (n = 53)  Placebo (n = 28) | 53  28 | 6  2 | 4.2 (-12.5,∞,16.6) | 24 (6,∞,-8) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Wagner KD, et al. (2009) [16] | DIV-ER 80-125 ug/ml (n = 77)  Placebo (n = 74) | 76  74 | 4  3 | 1.2 (-6.7,∞,9.2) | 83 (11,∞,-15) | n/a | n/a | n/a | n/a | 76  74 | 5  1 | 5.2 (-1.8,∞,13.2) | 19 (8,∞,-57) |
| Wagner KD, et al. (2006) [17] | OXC 900-2400mg/d (n = 59)  Placebo (n = 57) | 59  57 | 11  1 | **16.9 (6.0,28.7)** | **6 (3,17)** | n/a | n/a | n/a | n/a | 59  57 | 12  2 | **16.8 (5.0,29.0)** | **6 (3,20)** |
| Findling RL, et al. (2009) [18] | ARIP10 mg/d (n = 98)  ARIP 30 mg/d (n = 99)  Placebo (n = 99) | 98  99  99 | 4  7  1 | 3.1 (-2.1,∞,9.1)  **6.1 (0.3,12.9)** | 33 (11,∞,-49)  **17 (8,331)** | 98  99  97 | 3  9  3 | 0.0 (-6.0,∞,5.9)  6.0 (-1.0,∞,13.6) | -3169 (17,∞,-17)  17 (7,∞,-97) | 98  99  97 | 19  26  3 | **16.3 (7.6,25.4)**  **23.2 (13.7,32.8)** | **6 (4,13)**  **4 (4,7)** |
| Findling RL, et al. (2015) [19] | ASE 5 mg/d (n = 104)  ASE 10 mg/d (n = 99)  ASE 20 mg/d (n = 99)  Placebo (n = 101) | 104  99  99  101 | 7  5  5  4 | 2.8 (-4.0,∞,9.7)  1.1 (-5.4,∞,7.8)  1.1 (-5.4,∞,7.8) | 36 (10,∞,-25)  92 (13,∞,-19)  92 (13,∞,-19) | 92  90  87  89 | 11  8  7  1 | **10.8 (3.7,19.1)**  **7.8 (1.2,15.5)**  **6.9 (0.5,14.6)** | **9 (5,27)**  **13 (6,85)**  **14 (7,207)** | 104  99  99  101 | 34  34  31  6 | **26.8 (16.3,36.8)**  **28.4 (17.7,38.7)**  **25.4 (14.9,35.6)** | **4 (3,6)**  **4 (3,6)**  **4 (3,7)** |
| Tohen M, et al. (2007) [20] | OLA 2.5-20 mg/d (n = 107)  Placebo (n = 54) | 107  54 | 3  1 | 1.0 (-7.2,∞,6.3) | 105 (16,∞,-14) | 105  54 | 44  1 | **40.1 (28.1,49.7)** | **2 (2,4)** | n/a | n/a | n/a | n/a |
| Pathak S, et al. (2013) [21] | QTP-IR 400 mg/d (n = 95)  QTP-IR 600 mg/d (n = 98)  Placebo (n = 91) | 95  98  91 | 15  7  4 | **11.4 (2.7,20.4)**  2.8 (-4.6,∞,10.1) | **9 (5,38)**  36 (10,∞,-22) | n/a | n/a | n/a | n/a | 95  98  90 | 27  31  9 | **18.4 (7.1,29.2)**  **21.6 (10.1,32.4)** | **5 (3,14)**  **5 (3,10)** |
| Haas M, et al. (2009) [22] | RIS 0.5-2.5 mg/d (n = 50)  RIS 3-6 mg/d (n = 61)  Placebo (n = 58) | 50  61  58 | 3  10  4 | -0.9(-11.2,∞,10.1)  9.5 (-2.5,∞,21.5) | -112 (10,∞,-9)  11 (5,∞,-40) | 49  60  57 | 7  6  3 | 9.0 (-2.6,∞,21.9)  4.7 (-5.8,∞,15.5) | 11 (5,∞,-39)  21 (6,∞,-17) | 50  61  58 | 21  34  11 | **23.0 (5.7,39.0)**  **36.8 (19.6,51.0)** | **4 (3,18)**  **3 (2,5)** |
| Findling RL, et al. (2013) [23] | ZIP 40-160 mg/d (n = 149)  Placebo (n = 88) | 149  88 | 18  11 | -0.4 (-10.0,∞,7.8) | -238 (13,∞,-10) | 149  88 | 10  3 | 3.3 (-3.5,∞,9.0) | 30 (11,∞,-28) | 149  88 | 37  7 | **16.9 (7.1,25.4)** | **6 (4,14)** |
| **Bipolar Depression** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| DelBello MP, et al (2017) [24] | LUR 20-80 mg/d (n = 176)  Placebo (n = 174) | 176  174 | 3  3 | 0.0 (-3.4,∞,3.4) | -5104(30,∞,-29) | 162  157 | 6  8 | -1.4 (-6.4,∞,3.4) | -72 (29,∞,-16) | 175  172 | 20  10 | 5.6 (-0.4,∞,11.8) | 18 (8,∞,-258) |
| Detke HC, et al. (2015) [25] | OFC 6/25-12/50 mg/d (n =194)  Placebo (n = 97) | 170  85 | 24  5 | 8.2 (-0.2,∞,15.1) | 12 (7,∞,-524) | 170  85 | 88  3 | **48.2 (38.4,56.0)** | **2 (2,3)** | 170  85 | 27  2 | **13.5 (6.0,20.0)** | **7 (5,17)** |
| Findling RL, et al. (2014) [26] | QTP-XR 150-300 mg/d (n= 93)  Placebo (n = 100) | 92  100 | 3  12 | **-8.7 (-16.8,-1.0)** | **-11 (-99,-6)** | 88  100 | 11  6 | 6.5 (-1.9,∞,15.6) | 15 (6,∞,-52) | 92  100 | 6  4 | 2.5 (-4.3,∞,9.9) | 40 (10,∞,-23) |

Note: Significant difference of ARI and NNH between active treatment and its respective placebo was shown in bold.

Abbreviations: ARI, absolute risk increase; ARIP, aripiprazole; ASE, asenapine; CI, confidence interval; DIV, divalproex; ER&XR, extended release; IR, immediate release; LI, lithium; LUR, lurasidone; n/a, not available; NNH, number needed to harm; No., number; OFC, olanzapine/fluoxetine combination; OLA, olanzapine; OXC, oxcarbazepine; QTP, quetiapine; RIS, risperidone; ZIP, ziprasidone.

Supplementary Table 4 Single analysis of each randomized, double-blind, placebo-controlled trial for the risk of akathisia, nausea, and vomiting in the acute treatment of pediatric patients with bipolar disorder

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Treatment Arm** | **Akathisia** | | | | **Nausea** | | | | **Vomiting** | | | | |
| **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** | **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** | **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | | **NNH Mean**  **(95% CI)** |
| **Bipolar Mania** |  |  |  |  |  |  |  |  |  |  |  |  | |  |
| Findling RL, et al. (2015) [15] | Li < 1.4mEq/L (n = 53)  Placebo (n = 28) | n/a | n/a | n/a | n/a | 53  28 | 23  5 | **25.5 (3.9,42.2)** | **4 (2,26)** | 53  28 | 24  3 | **34.6 (13.8,49.6)** | | **3 (2,7)** |
| Wagner KD, et al. (2009) [16] | DIV-ER 80-125 ug/ml (n = 77)  Placebo (n = 74) | n/a | n/a | n/a | n/a | 76  74 | 7  1 | **7.9 (0.3,16.5)** | **13 (6, 313)** | 76  74 | 10  6 | 5.1(-5.2,∞,15.4) | | 20 (6,∞,-19) |
| Wagner K,D et al. (2006**)** [17] | OXC 900-2400mg/d (n = 59)  Placebo (n = 57) | n/a | n/a | n/a | n/a | 59  57 | 18  6 | **20.0 (5.2,33.8)** | **5 (3,19)** | 59  57 | 4  1 | 5.0 (-3.6,∞,14.5) | | 20 (7,∞,-28) |
| Findling RL, et al. (2009) [18] | ARIP 10 mg/d (n = 98)  ARIP 30 mg/d (n = 99)  Placebo (n = 99) | 98  99  97 | 8  11  2 | 6.1 (-0.4,∞,13.4)  **9.1 (2.0,16.9)** | 16 (7,∞,-251)  **11 (6,50)** | 98  99  97 | 9  12  4 | 5.1 (-2.3,∞,12.8)  **8.0 (0.2,16.3)** | 20 (8, -43)  **13 (6,656)** | 98  99  97 | 8  7  9 | -1.1 (-9.5,∞,7.2)  -2.2 (-10.5,∞,5.9) | | -90(14,∞,-10)  -45(17,∞,-10) |
| Findling RL, et al. (2015) [19] | ASE 5 mg/d (n = 104)  ASE 10 mg/d (n = 99)  ASE 20 mg/d (n = 99)  Placebo (n = 101) | 104  99  99  101 | 2  2  1  0 | 1.9 (-2.0,∞,6.7)  2.0 (-1.9,∞,7.1)  1.0 (-2.7,∞,5.5) | 52 (15,∞,-50)  50 (14,∞,-52)  99 (18,∞,-36) | 104  99  99  101 | 5  3  4  3 | 1.8 (-4.2,∞,8.1)  0.1 (-5.7,∞,5.9)  1.1 (-4.9,∞,7.3) | 54 (12,∞,-24)  1666 (17,∞,-18)  93 (14,∞,-21) | n/a | n/a | n/a | | n/a |
| Tohen M, et al. (2007) [20] | OLA 2.5-20 mg/d (n = 107)  Placebo (n = 54) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | | n/a |
| Pathak S, et al. (2013) [21] | QTP-IR 400 mg/d (n = 95)  QTP-IR 600 mg/d (n = 98)  Placebo (n = 91) | n/a | n/a | n/a | n/a | 95  98  90 | 6  10  4 | 1.9 (-5.4,∞,9.2)  5.8 (-2.1,∞,13.8) | 53 (11,∞,-19)  17 (7,∞,-47) | 95  98  90 | 8  7  3 | 5.1 (-2.2,∞,12.7)  3.8 (-3.2,∞,11.0) | | 20 (8,∞,-46)  26 (9,∞,-31) |
| Haas M, et al. (2009) [22] | RIS 0.5-2.5 mg/d (n = 50)  RIS 3-6 mg/d (n = 61)  Placebo (n = 58) | n/a | n/a | n/a | n/a | 50  61  58 | 8  8  4 | 9.1 (-3.1,∞,22.3)  6.2 (-5.2,∞,17.7) | 11 (4,∞,-32)  16 (6,∞,-19) | 50  61  58 | 6  6  4 | 5.1 (-6.4,∞,17.6)  2.9 (-8.0,∞,13.8) | | 20 (6,∞,-16)  34 (7,∞,-13) |
| Findling RL, et al. (2013) [23] | ZIP 40-160 mg/d (n = 149)  Placebo (n = 88) | 149  88 | 8  1 | 4.2 (-1.4,∞,9.2) | 24 (11,∞,-70) | 149  88 | 21  6 | 7.3 (-1.4,∞,14.7) | 14 (7,∞,-73) | 149  88 | 12  1 | **6.9 (0.9,12.5)** | | **14 (8,116)** |
| **Bipolar Depression** |  |  |  |  |  |  |  |  |  |  |  |  | |  |
| DelBello MP, et al (2017) [24] | LUR 20-80 mg/d (n = 176)  Placebo (n = 174) | 175  172 | 5  6 | -0.6 (-4.9,∞,3.5) | -158 (29,∞,-21) | 175  172 | 28  10 | **10.2 (3.7,16.9)** | **10 (6,27)** | 175  172 | 11  6 | 2.8 (-2.0,∞,7.8) | | 36 (13,∞,-51) |
| Detke HC, et al. (2015) [25] | OFC 6/25-12/50 mg/d (n =194)  Placebo (n = 97) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | 170  85 | 11  6 | -0.6 (-8.6,∞,5.5) | -170(18,∞,-12) | |
| Findling RL, et al. (2014) [26] | QTP-XR 150-300 mg/d (n= 93)  Placebo (n = 100) | n/a | n/a | n/a | n/a | 92  100 | 5  1 | 4.4 (-1.0,∞,11.2) | 23 (9,∞,-102) | n/a | n/a | n/a | | n/a |

Note: Significant difference of ARI and NNH between active treatment and its respective placebo was shown in bold.

Abbreviations: ARI, absolute risk increase; ARIP, aripiprazole; ASE, asenapine; CI, confidence interval; DIV, divalproex; ER&XR, extended release; IR, immediate release; LI, lithium; LUR, lurasidone; n/a, not available; NNH, number needed to harm; No., number; OFC, olanzapine/fluoxetine combination; OLA, olanzapine; OXC, oxcarbazepine; QTP, quetiapine; RIS, risperidone; ZIP, ziprasidone.

Supplementary Table 5 Single analysis of each randomized, double-blind, placebo-controlled trial for the risk of discontinuation due to adverse events, ≥ 7% weight gain, and somnolence in the acute treatment of adult patients with bipolar disorder

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Treatment Arm** | **Discontinuation Due to Adverse Events** | | | | **≥ 7% Weight Gain** | | | | **Self-Report Somnolence** | | | |
| **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** | **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** | **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** |
| **Bipolar Mania** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Lithium** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Keck PE, et al. (2009)**a** [27] | LI 0.60–1.20 mEq/L (n = 160)  Placebo (n = 165) | 160  165 | 20  13 | 4.6(-2.1,∞,11.5) | 22 (9,∞,-49) | 91  87 | 2  1 | 1.1 (-4.3,∞,6.6) | 95 (15,∞,-23) | n/a | n/a | n/a | n/a |
| Bowden CL, et al. (2005)**b** [28] | LI 0.60–1.40 mEq/L (n = 98)  Placebo (n = 97) | 98  97 | 6  4 | 2.0 (-4.9,∞,9.7) | 50 (11,∞,-21) | 98  97 | 14  8 | 6.0 (-3.1,∞,15.2) | 17 (7,∞,-33) | 98  97 | 9  3 | 6.1(-1.0,∞,13.7) | 16 (7,∞,-104) |
| **Divalproex** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hirschfeld RM, et al. (2010)[29] | DIV-ER 2000 mg/d (n = 147)  Placebo (n = 78) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | 147  78 | 21  5 | 7.9(-1.2,∞,15.4) | 13 (6,∞,-83) |
| Tohen M, et al. (2008) [30] | DIV-ER 50-125 ug/ml(n = 201)  Placebo (n = 105) | 201  105 | 6  1 | 2.0 (-2.5,∞,5.5) | 49 (18,∞,-40) | 188  100 | 5  1 | 1.7 (-0.3,∞,5.2) | 60 (19,∞,-33) | 201  105 | 5  3 | -0.4 (-5.8,∞,3.3) | -271 (30,∞,-17) |
| Bowden CL, et al. (2006) [31] | DIV-ER 85-125 ug/ml(n = 192)  Placebo (n = 185) | 192  185 | 19  6 | **6.7 (1.6,12.0)** | **15 (8,62)** | 192  185 | 17  6 | **5.6 (0.7,10.8)** | **18 (9,139)** | 192  185 | 64  26 | **19.3 (10.8,27.4)** | **5 (4,9)** |
| Bowden CL, et al. (1994) [32] | DIV-ER ≤ 150 ug/ml (n = 69)  Placebo (n = 74) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | 69  74 | 13  11 | 4.0(-8.4,∞,16.5) | 25 (6,∞,-12) |
| **Aripiprazole** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kanba S, et al. (2014) [33] | APRI 12-24 mg/d (n = 128)  Placebo (n =130) | 128  130 | 12  12 | 0.1 (-7.2,∞,7.5) | 693 (13,∞,-14) | 123  125 | 1  0 | 0.8 (-2.2,∞,4.5) | 123 (22,∞,-45) | n/a | n/a | n/a | n/a |
| El Mallakh RS, et al. (2010)[34] | APRI 15 mg/d (n = 131)  APRI 30 mg/d (n = 136)  Placebo (n = 134) | 131  136  134 | 20  9  9 | **8.6 (1.0,16.4)**  -0.1 (-6.5,∞,6.2) | **12 (6,103)**  -1012(16,∞,-15) | 131  135  133 | 3  8  7 | -3.0 (-8.4,∞,2.0)  0.7 (-5.3,∞,6.6) | -34 (49,∞,-12)  151 (15,∞,-19) | n/a | n/a | n/a | n/a |
| Young AH, et al. (2009) [35] | APRI 15-30 mg/d (n = 167)  Placebo (n = 153) | 167  153 | 14  16 | -6.5 (-8.8,∞,4.4) | -48 (23,∞,-11) | 156  140 | 3  9 | -4.5 (-1.0,∞,0.1) | -22 (588,∞,-10) | n/a | n/a | n/a | n/a |
| Keck PE, et al. (2009) [27] | APRI 15-30 mg/d (n = 155)  Placebo (n = 165) | 155  165 | 23  13 | 7.0 (-0.0,∞,14.2) | 14 (7,∞,-3427) | 93  87 | 1  1 | -0.1 (-5.2,∞,4.8) | -1349(21,∞,-19) | n/a | n/a | n/a | n/a |
| Sachs G, et al. (2006) [36] | APRI 15-30 mg/d (n = 137)  Placebo (n = 135) | 137  135 | 12  10 | 1.4 (-5.4,∞,8.2) | 74 (12,∞,-18) | 125  119 | 1  5 | -3.4 (-8.7,∞,0.9) | -29 (109,∞,-11) | 136  133 | 27  14 | **9.3 (0.7,17.9)** | **11 (6,145)** |
| Keck PE Jr, et al. (2003) [37] | APRI 15-30 mg/d (n = 130)  Placebo (n = 132) | 130  132 | 14  13 | 0.9 (-6.7,∞,8.6) | 109 (12,∞,-15) | 127  127 | 2  0 | 1.6 (-1.6,∞,5.7) | 64 (18,∞,-63) | 127  127 | 26  6 | **15.8 (7.7,24.0)** | **6 (4,13)** |
| **Asenapine** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Landbloom RL, et al. (2016) [38] | ASE 10 mg/d (n = 122)  ASE 20 mg/d (n = 119)  Placebo (n = 126) | 122  119  126 | 13  10  9 | 3.5 (-3.8,∞,11.0)  1.3 (-5.7,∞,8.5) | 28 (9,∞,-26)  79 (12,∞,-17) | 122  119  126 | 8  1  0 | **6.6 (2.2,12.4)**  0.8 (-2.2,∞,4.6) | **15 (8,45)**  119 (22,∞,-45) | 122  119  126 | 12  14  3 | **7.5 (1.4,14.2)**  **9.4(3.0,16.6)** | **13 (7,70)**  **11 (6,33)** |
| McIntyre RS, et al. (2010) [39] | ASE 10-20 mg/d (n = 185)  Placebo (n = 98) | 185  98 | 17  4 | 5.1 (-1.7,∞,10.7) | 20 (19,∞,-58) | 185  98 | 13  1 | **6.0 (0.6,10.7)** | **17 (9,157)** | 185  98 | 22  3 | **8.8 (2.4,14.7)** | **11 (7,49)** |
| McIntyre RS, et al. (2009) [40] | ASE 10-20 mg/d (n = 194)  Placebo (n = 105) | 194  104 | 20  7 | 3.6 (-3.8,∞,9.7) | 28 (10,∞,-26) | 194  105 | 12  0 | **6.2 (1.8,10.5)** | **16 (10,56)** | 194  105 | 17  2 | **6.1 (1.1,11.9)** | **15 (8,91)** |
| **Olanzapine** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Katagiri H, et al. (2012) [41] | OLA 5-20 mg/d (n = 105)  Placebo (n = 99) | 105  99 | 9  7 | 1.5 (-6.4,∞,9.3) | 67 (11,∞,-16) | 105  96 | 7  1 | 5.6 (-0.1,∞,12.1) | 18 (8,∞,-868) | 105  96 | 21  8 | **11.7 (1.9,21.2)** | **9 (5,53)** |
| McIntyre RS, et al. (2010) [39] | OLA 5-20 mg/d (n = 205)  Placebo (n = 98) | 205  98 | 7  4 | -0.7 (-6.9,∞,3.6) | -150 (28,∞,-15) | 205  98 | 39  1 | **18.0(11.4,24.0)** | **6 (4,9)** | 205  98 | 23  3 | **8.2 (1.5,13.6)** | **12 (7,66)** |
| McIntyre RS, et al. (2009) [40] | OLA 5-20 mg/d (n = 190)  Placebo (n = 105) | 190  104 | 8  7 | -2.5 (-9.4,∞,2.7) | -40 (38,∞,-11) | 189  105 | 24  0 | **12.7(7.4,18.2)** | **8 (5,14)** | 189  105 | 14  2 | 5.5(-0.1,∞,10.3) | 18 (10,∞,-929) |
| Tohen M, et al. (2008) [30] | OLA 5-20 mg/d (n = 215)  Placebo (n = 105) | 215  105 | 16  1 | **6.5 (1.4,10.9)** | **15 (9,72)** | 202  100 | 13  1 | **5.4 (0.3,9.8)** | **18 (10,378)** | 215  105 | 19  3 | 6.0(-0.1,∞,10.9) | 17 (9,∞,-1182) |
| Tohen M, et al. (2000) [42] | OLA 5-20 mg/d (n = 55)  Placebo (n = 60) | 55  60 | 2  1 | 2.0 (-5.7,∞,10.8) | 51 (9,∞,-18) | n/a | n/a | n/a | n/a | 55  60 | 21  5 | **29.9 (14.7,43.9)** | **3 (2,7)** |
| Tohen M, et al. (1999) [43] | OLA 5-20 mg/d (n = 70)  Placebo (n = 69) | 70  69 | 0  2 | -2.9 (-10.0,∞,2.7) | -35 (37,∞,-10) | n/a | n/a | n/a | n/a | 70  69 | 23  12 | **15.5 (1.0,29.3)** | **6 (3,100)** |
| **Quetiapine** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Vieta E, et al. (2010)c [44] | QTP-IR 400-800 mg/d (n= 193)  Placebo (n = 105) | 193  105 | 4  5 | -2.7 (-8.7,∞,1.5) | -37 (69,∞,-11) | n/a | n/a | n/a | n/a | 192  105 | 35  4 | **14.4(7.1,20.9)** | **7 (5,14)** |
| McIntyre RS, et al. (2005)d[45] | QTP-IR 400-800 mg/d (n= 102)  Placebo (n = 101) | 102  101 | 5  6 | -1.0 (-8.0,∞,5.8) | -96 (17,∞,-12) | 102  101 | 13  4 | **8.8 (1.1, 17.0)** | **11 (6,96)** | 102  101 | 13  5 | 7.8(-0.2,∞,16.1) | 13 (6,∞,-503) |
| Bowden CL, et al. (2005)d [28] | QTP-IR 400-800 mg/d (n= 107)  Placebo (n = 97) | 107  97 | 7  4 | 2.4 (-4.5,∞,9.3) | 41 (11,∞,-22) | 107  97 | 31  8 | **20.7 (10.2,30.8)** | **5 (3,10)** | 107  97 | 21  3 | **16.5 (8.0,25.3)** | **6 (4,12)** |
| **Risperidone** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Smulevic AB, et al. (2005) [46] | RIS 1-6 mg/d (n = 154)  Placebo (n = 140) | 154  140 | 6  7 | -1.1 (-6.5,∞,3.9) | -91 (25,∞,-15) | n/a | n/a | n/a | n/a | 154  140 | 7  2 | 3.1 (-1.2,∞,7.8) | 32 (13,∞,-84) |
| Khanna S, et al. (2005) [47] | RIS 1-6 mg/d (n = 146)  Placebo (n = 145) | 146  145 | 5  3 | 1.4 (-3.0,∞,5.9) | 74 (17,∞,-34) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Hirschfeld RM, et al. (2004) [48] | RIS 1-6 mg/d (n = 134)  Placebo (n = 125) | 134  125 | 10  7 | 1.9 (-4.6,∞,8.3) | 54 (12,∞,-22) | 134  125 | 5  0 | **3.7 (0.1,8.4)** | **27 (12,1454)** | 134  125 | 38  9 | **21.2 (12.0,30.0)** | **5 (3,8)** |
| **Ziprasidone** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Vieta E, et al. (2010) [49] | ZIP 80-160 mg/d (n = 178)  Placebo (n = 88) | 178  88 | 17  4 | 5.0 (-2.4,∞,10.9) | 20 (9,∞,-41) | 178  88 | 17  2 | **7.3 (0.6,12.7)** | **14 (8,156)** | 178  88 | 1  3 | -2.9 (-9.0,∞,0.6) | -35 (182,∞,-11) |
| Potkin SG, et al. (2005) [50] | ZIP 80-160 mg/d (n = 140)  Placebo (n = 66) | 140  66 | 8  1 | 4.2 (-3.0,∞,9.5) | 24 (11,∞,-34) | 125  59 | 6  2 | 1.4 (-7.1,∞,7.2) | 71 (14,∞,-14) | 139  66 | 31  4 | **16.2 (5.8,24.7)** | **6 (4,17)** |
| Keck PE Jr, et al. (2003) [51] | ZIP 80-160 mg/d (n = 140)  Placebo (n = 70) | 140  70 | 9  3 | 2.1 (-6.0,∞,8.2) | 47 (12,∞,-17) | n/a | n/a | n/a | n/a | 140  70 | 52  9 | **24.3 (11.9,34.5)** | **4 (3,8)** |
| **Bipolar Depression** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Lurasidone** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Loebel A, et al. (2014) [52] | LUR 20-60 mg/d (n = 166)  LUR 80-120 mg/d (n=169)  Placebo (n = 170) | 166  169  170 | 11  10  11 | 0.2 (-5.4,∞,5.8)  -0.6 (-6.0,∞,4.9) | 641 (17,∞,-19)  -181 (21,∞,-17) | 164  167  168 | 7  1  1 | **3.7 (0.2,8.0)**  0.0 (-2.7,∞,2.8) | **27 (13,500)**  28056 (36,∞,-36) | 164  167  168 | 7  11  7 | 0.1 (-4.6,∞,4.9)  2.4 (-2.7,∞,7.7) | 984 (20,∞,-22)  41 (13,∞,-38) |
| **Olanzapine/fluoxetine combination** | |  |  |  |  |  |  |  |  |  |  |  |  |
| Tohen M, et al. (2003) [53] | OFC 6/25-12/50 mg/d (n = 86)  Placebo (n = 377) | 86  377 | 2  19 | -2.7 (-5.9,∞,3.3) | -37 (30,∞,-17) | 82  355 | 16  1 | **19.2(12.0,29.1)** | **5 (3,8)** | 86  377 | 18  47 | **8.5 (0.3,18.7)** | **12 (5,326)** |
| **Quetiapine** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Murasaki M, et al. (2018) [54] | QTP-XR 150 mg/d (n = 74)  QTP-XR 300 mg/d (n = 179)  Placebo (n = 177) | 74  179  177 | 6  27  16 | -0.9 (-7.7,∞,8.2)  6.0 (-0.8,∞,12.9) | -107 (12,∞,-13)  17 (8,∞,-127) | n/a | n/a | n/a | n/a | 74  179  177 | 26  80  4 | **32.9 (22.4,44.3)**  **42.4 (34.6,50.0)** | **3 (2,4)**  **2 (2,3)** |
| Li H, et al. (2016) [55] | QTP -XR 300 mg/d (n = 148)  Placebo (n = 148) | 147  147 | 9  8 | 0.7 (-5.0,∞,6.4) | 147 (16,∞,-20) | 147  147 | 13  4 | **6.1 (0.7,12.1)** | **16 (8,145)** | 147  147 | 36  11 | **17.0 (8.7,25.2)** | **6 (4,11)** |
| Suppes T, et al. (2010) [56] | QTP-XR 300 m/d (n = 140)  Placebo (n = 140) | 140  140 | 17  2 | **10.7 (5.0,17.2)** | **9 (6,20)** | 137  140 | 9  1 | **5.9 (1.4,11.3)** | **17 (9,71)** | 137  140 | 40  8 | **23.5 (14.8,32.1)** | **4 (3,7)** |

Note: Significant difference of ARI and NNH between active treatment and its respective placebo was shown in bold.

a. The study duration of lithium was 3 weeks. b. The study duration of lithium was 12 weeks. c. The study duration of quetiapine-IR was 3 weeks. d. Quetiapine-IR was studied in two separately 12-week studies.

Abbreviations: ARI, absolute risk increase; ARIP, aripiprazole; ASE, asenapine; CI, confidence interval; DIV, divalproex; ER&XR, extended release; IR, immediate release; LI, lithium; LUR, lurasidone; n/a, not available; NNH, number needed to harm; No. number; OFC, olanzapine/fluoxetine combination; OLA, olanzapine; QTP, quetiapine; RIS, risperidone; ZIP, ziprasidone.

Supplementary Table 6 Single analysis of each randomized, double-blind, placebo-controlled trial for the risk of akathisia, nausea, and vomiting in the acute treatment of adult patients with bipolar disorder

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Treatment Arm** | **Akathisia** | | | | **Nausea** | | | | **Vomiting** | | | |
| **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** | **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** | **Total No.** | **No. of cases** | **ARI Mean**  **(95% CI)** | **NNH Mean**  **(95% CI)** |
| **Bipolar Mania** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Lithium** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Keck PE, et al. (2009)**a** [27] | LI 0.60–1.20 mEq/L (n = 160)  Placebo (n = 165) | 159  164 | 8  5 | 2.0 (-2.6,∞,6.9) | 50 (15,∞,-38) | 159  164 | 37  22 | **9.9 (1.4,18.2)** | **10 (5,71))** | n/a | n/a | n/a | n/a |
| Bowden CL, et al. (2005)**b** [28] | LI 0.60–1.40 mEq/L (n = 98)  Placebo (n = 97) | 98  97 | 3  6 | -3.1 (-10.1,∞,3.3) | -32 (30,∞,-10) | 98  97 | 6  2 | 4.1 (-2.0,∞,10.8) | 25 (9,∞,-49) | 98  97 | 6  2 | 4.1(-2.0,∞,10.8) | 25 (9,∞,-49) |
| **Divalproex** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hirschfeld RM, et al. (2010) [29] | DIV-ER 2000 mg/d (n = 147)  Placebo (n = 78) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Tohen M, et al. (2008) [30] | DIV-ER 50-125 ug/ml (n= 201)  Placebo (n = 105) | n/a | n/a | n/a | n/a | 201  105 | 17  3 | 5.6 (-0.5,∞,10.6) | 18 (9,∞,-215) | n/a | n/a | n/a | n/a |
| Bowden CL, et al. (2006) [31] | DIV-ER 85-125 ug/ml (n= 192)  Placebo (n = 185) | n/a | n/a | n/a | n/a | 192  185 | 53  28 | **12.2 (3.9,20.3)** | **8 (5,26)** | 192  185 | 35  12 | **11.6 (5.0,18.3)** | **9 (5,20)** |
| Bowden CL, et al. (1994) [32] | DIV-ER ≤ 150 ug/ml (n = 69)  Placebo (n = 74) | n/a | n/a | n/a | n/a | 69  74 | 16  11 | 8.3 (-4.6,∞,21.2) | 12 (5,∞,-22) | 69  74 | 10  3 | **10.4 (0.8,21.0)** | **10 (5,127)** |
| **Aripiprazole** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kanba S, et al. (2014) [33] | APRI 12-24 mg/d (n = 128)  Placebo (n =130) | 123  125 | 27  7 | **16.4 (7.9,24.9)** | **6 (4,13)** | 123  125 | 10  5 | 4.1 (-2.1,∞,10.7) | 24 (9,∞,-48) | 123  125 | 15  6 | **7.4 (0.4,14.8)** | **14 (7,284)** |
| El Mallakh RS, et al. (2010) [34] | APRI 15 mg/d (n = 131)  APRI 30 mg/d (n = 136)  Placebo (n = 134) | 131  135  133 | 18  15  3 | **11.5 (5.1,18.6)**  **8.9 (2.9,15.4)** | **9 (5,20)**  **11 (6,35)** | 131  135  133 | 23  18  19 | 3.3 (-5.6,∞,12.2)  -1.0 (-9.4,∞,7.4) | 31 (8,∞,-18)  -105 (13,∞,-11) | 131  135  133 | 14  7  3 | **8.4 (2.5,15.1)**  2.9 (-2.0,∞,8.3) | **12 (7,40)**  34 (12,∞,-50) |
| Young AH, et al. (2009) [35] | APRI 15-30 mg/d (n = 167)  Placebo (n = 153) | 166  153 | 15  7 | 4.5 (-1.3,∞,10.3) | 22 (10,∞,-78) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Keck PE, et al. (2009) [27] | APRI 15-30 mg/d (n = 155)  Placebo (n = 165) | 154  164 | 17  5 | **8.0 (2.4,14.2)** | **13 (7,42)** | 154  164 | 35  22 | **9.3 (0.8,17.8)** | **11 (6,118)** | n/a | n/a | n/a | n/a |
| Sachs G, et al. (2006) [36] | APRI 15-30 mg/d (n = 137)  Placebo (n = 135) | 136  133 | 24  6 | **13.1 (5.7,20.8)** | **8 (5,17)** | 136  133 | 29  21 | 5.5 (-3.8,∞,14.8) | 18 (7,∞,-26) | 136  133 | 15  10 | 3.5(-3.6,∞,10.7) | 28 (9,∞,-27) |
| Keck PE Jr, et al. (2003) [37] | APRI 15-30 mg/d (n = 130)  Placebo (n = 132) | 127  127 | 14  3 | **8.7 (2.5,15.5)** | **12 (6,40)** | 127  127 | 29  13 | **12.6 (3.5,21.6)** | **8 (5,29)** | 127  127 | 20  6 | **11.0 (3.6,18.8)** | **9 (5,28)** |
| **Asenapine** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Landbloom RL, et al. (2016) [38] | ASE 10 mg/d (n = 122)  ASE 20 mg/d (n = 119)  Placebo (n = 126) | 122  119  126 | 5  18  1 | 3.3 (-1.0,∞,8.5)  **14.3 (7.9,21.9)** | 30 (12,∞,-104)  **7 (5,13)** | 122  119  126 | 4  6  4 | 0.1 (-5.0,∞,5.3)  1.9 (-3.6,∞,7.7) | 961 (19,∞,-20)  54 (13,∞,-28) | 122  119  126 | 1  4  2 | -0.8 (-4.8,∞,3.1)  1.8 (-2.7,∞,6.9) | -130 (32,∞,-21)  56 (15,∞,-37) |
| McIntyre RS, et al. (2010) [39] | ASE 10-20 mg/d (n = 185)  Placebo (n = 98) | 185  98 | 10  3 | 2.3 (-3.7,∞,7.1) | 43 (14,∞,-27) | n/a | n/a | n/a | n/a | 185  98 | 10  2 | 3.4 (-2.3,∞,7.9) | 30 (13,∞,-44) |
| McIntyre RS, et al. (2009) [40] | ASE 10-20 mg/d (n = 194)  Placebo (n = 105) | 194  105 | 5  2 | 0.7 (-4.3,∞,4.3) | 149 (23,∞,-23) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Olanzapine** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Katagiri H, et al. (2012) [41] | OLA 5-20 mg/d (n = 105)  Placebo (n = 99) | 105  96 | 2  0 | 1.9 (-2.2,∞,6.7) | 53 (15,∞,-46) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| McIntyre RS, et al. (2010) [39] | OLA 5-20 mg/d (n = 205)  Placebo (n = 98) | 205  98 | 10  3 | 1.8 (-4.2,∞,6.2) | 55 (16,∞,-24) | n/a | n/a | n/a | n/a | 205  98 | 4  2 | -0.1 (-5.3,∞,3.2) | -1116(31,∞,-19) |
| McIntyre RS, et al. (2009) [40] | OLA 5-20 mg/d (n = 190)  Placebo (n = 105) | 189  105 | 11  2 | 3.9 (-1.5,∞,8.4) | 26 (12,∞,-67) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Tohen M, et al. (2008) [30] | OLA 5-20 mg/d (n = 215)  Placebo (n = 105) | n/a | n/a | n/a | n/a | 215  105 | 2  3 | -1.9 (-7.2,∞,1.1) | -52 (89,∞,-14) | n/a | n/a | n/a | n/a |
| Tohen M, et al. (2000) [42] | OLA 5-20 mg/d (n = 55)  Placebo (n = 60) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Tohen M, et al. (1999) [43] | OLA 5-20 mg/d (n = 70)  Placebo (n = 69) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Quetiapine** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Vieta E, et al. (2010)c [44] | QTP-IR 400-800 mg/d (n= 193)  Placebo (n = 105) | 192  105 | 6  3 | 0.3 (-5.2,∞,4.3) | 373 (23,∞,-19) | 193  105 | 3  13 | **-10.8(-18.6,-5.0)** | **-9 (-20,-5)** | n/a | n/a | n/a | n/a |
| McIntyre RS, et al. (2005)d[45] | QTP-IR 400-800 mg/d (n= 102)  Placebo (n = 101) | 102  101 | 6  6 | -0.1 (-7.2,∞,7.1) | -1717(14,∞,-14) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Bowden CL, et al. (2005)d [28] | QTP-IR 400-800 mg/d (n= 107)  Placebo (n = 97) | 107  97 | 1  6 | -5.3 (-12.0,∞,0.1) | -19 (1257,∞,-8) | 107  97 | 1  2 | -1.1 (-6.3,∞,3.3) | -89 (30,∞,-16) | 107  97 | 1  2 | -1.1 (-6.3,∞,3.3) | -89 (30,∞,-16) |
| **Risperidone** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Smulevic AB, et al. (2005) [46] | RIS 1-6 mg/d (n = 154)  Placebo (n = 140) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Khanna S, et al. (2005) [47] | RIS 1-6 mg/d (n = 146)  Placebo (n = 145) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Hirschfeld RM, et al. (2004) [48] | RIS 1-6 mg/d (n = 134)  Placebo (n = 125) | n/a | n/a | n/a | n/a | 134  125 | 15  3 | **8.8 (2.6,15.4)** | **11 (6,38)** | n/a | n/a | n/a | n/a |
| **Ziprasidone** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Vieta E, et al. (2010)[49] | ZIP 80-160 mg/d (n = 178)  Placebo (n = 88) | 178  88 | 31  3 | **14.0 (6.2,20.6)** | **7 (5,16)** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Potkin SG, et al. (2005) [50] | ZIP 80-160 mg/d (n = 140)  Placebo (n = 66) | 139  66 | 13  3 | 4.8 (-4.0,∞,11.5) | 21 (9,∞,-25) | 139  66 | 9  1 | 5.0 (-2.3,∞,10.5) | 20 (10,∞,-44) | n/a | n/a | n/a | n/a |
| Keck PE Jr, et al. (2003) [51] | ZIP 80-160 mg/d (n = 140)  Placebo (n = 70) | 140  70 | 15  4 | 3.1 (-5.7,∞,9.4) | 32 (11,∞,-18) | 140  70 | 16  7 | 1.4 (-8.7,∞,9.5) | 70 (10,∞,-11) | n/a | n/a | n/a | n/a |
| **Bipolar Depression** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Lurasidone** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Loebel A, et al. (2014) [52] | LUR 20-60 mg/d (n = 166)  LUR 80-120 mg/d (n=169)  Placebo (n = 170) | 164  167  168 | 13  18  4 | **5.6 (0.7,10.9)**  **8.4 (3.1,14.2)** | **18 (9,139)**  **12 (7,32)** | 164  167  168 | 17  29  13 | 2.6 (-3.7,∞,9.1)  **9.6 (2.5,16.8)** | 38 (11,∞,-27)  **10 (6,40)** | 164  167  168 | 4  10  3 | 0.7 (-3.0,∞,4.5)  4.2 (-0.1,∞,9.0) | 153 (22,∞,-33)  24 (11,∞,-1130) |
| **Olanzapine/fluoxetine combination** | |  |  |  |  |  |  |  |  |  |  |  |  |
| Tohen M, et al. (2003) [53] | OFC 6/25-12/50 mg/d (n = 86)  Placebo (n = 377) | n/a | n/a | n/a | n/a | 86  377 | 10  33 | 2.9 (-3.3,∞,11.7) | 35 (9,∞,-31) | n/a | n/a | n/a | n/a |
| **Quetiapine** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Murasaki M, et al. (2018) [54] | QTP-XR 150 mg/d (n = 74)  QTP -XR 300 mg/d (n = 179)  Placebo (n = 177) | 74  179  177 | 7  15  4 | **7.2 (1.3,16.1)**  **6.1 (1.4,11.3)** | **14 (6,76)**  **16 (9,70)** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Li H, et al. (2016) [55] | QTP -XR 300 mg/d (n = 148)  Placebo (n = 148) | n/a | n/a | n/a | n/a | 147  147 | 3  10 | -4.8 (-10.2,∞,0.1) | -21 (903,∞,-10) | n/a | n/a | n/a | n/a |
| Suppes T, et al. (2010) [56] | QTP-XR 300 m/d (n = 140)  Placebo (n = 140) | n/a | n/a | n/a | n/a | 137  140 | 10  10 | 0.2 (-6.3,∞,6.6) | 639 (15,∞,-16) | n/a | n/a | n/a | n/a |

Note: Significant difference of ARI and NNH between active treatment and its respective placebo was shown in bold.

a. The study duration of lithium was 3 weeks. b. The study duration of lithium was 12 weeks. c. The study duration of quetiapine-IR was 3 weeks. d. Quetiapine-IR was studied in two separately 12-week studies.

Abbreviations: ARI, absolute risk increase; ARIP, aripiprazole; ASE, asenapine; CI, confidence interval; DIV, divalproex; ER&XR, extended release; IR, immediate release; LI, lithium; LUR, lurasidone; n/a, not available; NNH, number needed to harm; No., number; OFC, olanzapine/fluoxetine combination; OLA, olanzapine; QTP, quetiapine; RIS, risperidone; ZIP, ziprasidone.