**Supplementary materials to Kishimoto et al.
Efficacy and safety/tolerability of antipsychotics in the treatment of adult patients with major depressive disorder: A systematic review and meta-analysis.**

***Psychological Medicine***

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**Table S1 Risk of bias summary**

|  | ***Random sequence generation*** | ***Allocation concealment*** | ***Blinding of participants and personnel*** | ***Blinding of outcome assessment*** | ***Incomplete outcome data addressed*** | ***Selective reporting*** | ***Other sources of bias*** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Monotherapy |
| Bortnick 2011 | **?** | **?** | **low** | **low** | **low** | **low** | **low** |
| Boyer 1999 | **?** | **?** | **low** | **low** | **low** | **low** | **low** |
| Chaput 2008 | **?** | **low** | **low** | **low** | **high** | **low** | **?** |
| Cutler 2009 | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Frolund 1974 | **?** | **?** | **low** | **low** | **low** | **?** | **low** |
| Katila 2013 | **low** | **?** | **low** | **low** | **low** | **low** | **low** |
| Kennedy 2014 | **?** | **?** | **low** | **low** | **high** | **?** | **low** |
| Lecrubier 1997 | **?** | **?** | **low** | **low** | **high** | **low** | **low** |
| Liebowitz 2010 | **?** | **?** | **low** | **low** | **high** | **low** | **low** |
| Papakostas 2012 | **?** | **?** | **low** | **low** | **low** | **low** | **high** |
| Rüther 1999 | **?** | **?** | **low** | **low** | **low** | **low** | **low** |
| Wang 2014 | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Weisler 2009 | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Adjunctive therapy |
| Bauer 2009 | **?** | **?** | **low** | **low** | **low** | **low** | **low** |
| Berman 2007 | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Berman 2009 | **?** | **?** | **low** | **low** | **low** | **low** | **low** |
| Dunner 2007 | **?** | **?** | **high** | **high** | **high** | **low** | **low** |
| Durgam 2016 | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| El-Khalili 2010 | **low** | **?** | **low** | **low** | **low** | **low** | **low** |
| Fava 2012 | **?** | **?** | **low** | **low** | **low** | **low** | **high** |
| Flint 2019 | **low** | **?** | **low** | **low** | **low** | **low** | **low** |
| Garakani 2008 | **?** | **?** | **low** | **low** | **?** | **low** | **low** |
| Hobart 2018a | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Hobart 2018b | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Ionesc 2016 | **?** | **?** | **low** | **low** | **high** | **low** | **high** |
| Kamijima 2013 | **?** | **?** | **low** | **low** | **low** | **low** | **low** |
| Kamijima 2018 | **?** | **?** | **low** | **low** | **low** | **low** | **low** |
| Keitner 2009 | **?** | **?** | **low** | **low** | **?** | **high** | **low** |
| Lenze 2015 | **low** | **?** | **low** | **low** | **low** | **low** | **low** |
| Li 2016 | **?** | **?** | **low** | **low** | **high** | **low** | **high** |
| Lin 2011 | **?** | **?** | **low** | **low** | **high** | **low** | **low** |
| Mahmoud 2007 | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Marcus 2008 | **?** | **?** | **low** | **low** | **low** | **low** | **low** |
| McIntyre 2007 | **?** | **?** | **low** | **low** | **high** | **high** | **low** |
| Papakostas 2015 | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Parker 2005 | **?** | **?** | **low** | **high** | **?** | **high** | **high** |
| Quante 2013 | **?** | **?** | **low** | **low** | **?** | **low** | **low** |
| Reeves 2008 | **?** | **?** | **low** | **low** | **?** | **low** | **low** |
| Sim 1978 | **?** | **?** | **low** | **low** | **?** | **low** | **low** |
| Stabl 1995 | **?** | **?** | **low** | **low** | **?** | **low** | **low** |
| Thase 2015a | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Thase 2015b | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| Wade 2011 | **low** | **low** | **low** | **low** | **low** | **low** | **low** |
| NCT00797966 | **?** | **?** | **low** | **low** | **low** | **?** | **low** |
| NCT01052077 | **?** | **?** | **low** | **low** | **low** | **?** | **low** |

Risk of bias summary: review authors' judgements about each risk of bias item for each included study

(“low”: low risk of bias; “?”: unclear risk of bias; “high“: high risk of bias)

**Table S2 Characteristics of included studies**

| **Study/****Country/****Blinding status** | **Total no. of patients** | **Duration (weeks)** | **Patient characteristics****Diagnosis****Age** | **Continuation****treatment(s)** | **Treatment arms (n)** | **Mean age (years)** | **% Male** | **% White** | **Mean dose (mg/day)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Monotherapy*** |
| Bortnick 2011 (1)USDB | 310 | 8 | Diagnosis: MDD (DSM-IV), Age: 18-65 years, Severity: HAM-D-17 ≥ 22 and a HAM-D Item 1 (depressed mood) score ≥ 2 | None | QUE (154)PBO (156) | 43.342.6 | 35.435.5 | 68.765.8 | 162.2 |
| Boyer 1999 (2)FranceDB | 323 | 12 | Diagnosis: Primary dysthymia (DSM-III-R)Age: ≥ 18 yearsSeverity: MADRS < 21 | None | AMI (104)[AMIN (111)]PBO (108) | 484848 | 29.821.624.1  | 99.098.299.1  | AMI 50 and AMIN 200 fixed dose |
| Chaput 2008 (3)CanadaDB | 22 | 12 | Diagnosis: MDD (DSM-IV)Age: 23-66 yearsSeverity: HAM-D-21 ≥ 18, CGI-S score ≥ 4, treatment refractory depression | None | QUE (11)PBO (11) | 41.644.9 | 27.327.3  | NR | 147.7 |
| Cutler 2009 (4)USDB | 612 | 6 | Diagnosis: MDD (DSM-IV)Age: 18-65 years, Severity: HAM-D-17 ≥ 22 and HAM-D Item 1 score ≥ 2 | None | QUE 150 (152)QUE 300 (152)[Duloxetine 60 (151)]PBO (157) | 40.941.640.242.3  | 36.749.037.635.5 | 75.574.875.969.1  | QUE: 150 and 300 fixed doseDuloxetine: 60 fixed dose |
| Frolund 1974 (5)DenmarkDB | 231 | 2 | Diagnosis: Depression (clinical diagnosis)Age: 20-70 yearsSeverity: NR | None | FLU (120)PBO (111) | NR | 1520 | NR | 0.5 – 1.5 |
| Katila 2013 (6)MultiDB | 338 | 9 | Diagnosis: MDD (DSM-IV) Age: ≥ 66 yearsSeverity: HAM-D-17 ≥ 22 and HAM-D Item 1 score ≥ 2 | None | QUE (166)PBO (172) | 71.371.2 | 29.929.8 | 98.898.2 | 158.7 |
| Kennedy 2014 (7)CanadaDB | 53 | 1 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D-17 > 14 | None | HAL (26)PBO (27) | NR | NR | NR | 0.25 |
| Lecrubier 1997 (8)FranceDB | 219 | 24 | Diagnosis: Primary dysthymia with major depression (DSM-III-R)Age: NRSeverity: Mild or moderate severity or isolated chronic major depression in partial remission | None | AMI (73)[IMI (73)]PBO (73) | 41.844.042.9 | 43.852.139.7 | NR | AMI 50 and IMI 100 fixed dose |
| Liebowitz 2010 (9)MultiDB | 776 | 52 | Diagnosis: MDD (DSM-IV TR)Age: 18-65 yearsSeverity: MADRS score ≤ 12 and CGI-S score ≤ 3 | None | QUE (391)PBO (385) | 45.443.8 | 34.133.9 | NR | 177.1 |
| Papakostas 2012 (10)USDB | 120 | 12 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: QIDS-SR ≥ 10 | None | ZIP-ZIP (29) a)PBO-ZIP (47) a)PBO-PBO (44) a) | 41.544.144.6 | 55.261.750.0 | NR | Phase I 81.4Phase II 113.8 |
| Rüther 1999 (11)Germany and AustriaDB | 177 | 6 | Diagnosis: Depressive syndrome (ICD-10: F32.0, F32.1, F33.0, F33.1)Age: 18-70 yearsSeverity: 27 ≥ HAM-D-21 ≥ 18 | None | SUL (87)PBO (90) | 49.151.2 | 30.130.7 | NR | 181 |
| Wang 2014 (12)MultiDB | 471 | 8 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 22 and HAM-D Item 1 ≥ 2 | None | QUE (157)[ESC (157)]PBO (157) | 40.140.339.7 | 28.624.332.7 | 55.852.654.9 | QUE: 139.8ESC: 10.7 |
| Weisler 2009 (13)USDB | 723 | 6 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 22 and HAM-D Item 1 ≥2 | None | QUE 50 (182)QUE 150 (178)QUE 300 (179)PBO (184) | 40.641.540.740.3 | 46.638.141.536.5  | 73.673.869.976.4 | 50, 150 and 300 fixed dose |
| **- Number of studies:** 13 studies (13 reports)**- Number of patients:** 4,375[median=310 (range = 22−776)]**- Country:**US (studies=4, n=1,765)Multinational (studies=4, n=1,762)Canada (studies=2, n=75)France (studies=2, n=542)Denmark (study=1, n=231) | **- Blinding status:**DB (studies=13, n=4,375)**- Mean duration:** 12.2 weeks (range **=** 1 − 52)**- Antipsychotics:** AMI (studies=2, n=542), FLU (study=1, n=231), HAL (study=1, n=53), QUE (studies=7, n=3,252), SUL (study=1, n=177), ZIP (study=1, n=120) | **- Age:** 45.2±7.6 (range=39.7 – 71.3) years**- Gender** (Male 35.4%)**- Race** (White 76.7%) |
| ***Adjunctive therapy*** |
| Bauer 2009 (14)MultiDB | 493 | 6 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 20, HAM-D Item 1 score ≥2, and history of an inadequate response during the current episode | AD | QUE 150 (167)QUE 300 (163)PBO (163) | 46.045.544.8 | 30.731.735.0 | 99.496.998.1  | 150 and 300 fixed dose |
| Berman 2007 (15)USDB | 362 | 6 | Diagnosis: MDD (DSM-IV),Age: 18-65 yearsSeverity: HAM-D-17 ≥ 18, and inadequate response to AD treatment | AD | ARI (182)PBO (176) | 46.544.2 | 38.535.8 | 87.492.6 | 11.8 |
| Berman 2009 (16)USDB | 349 | 6 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: Inadequate response to AD | AD | ARI (177)PBO (172) | 45.145.6 | 22.032.0 | 87.686.6 | 10.7 |
| Dunner 2007 (17)USOL | 61 | 8 | Diagnosis: MDD (DSM-IV)Age: 21-65 yearsSeverity: MADRS > 14, CGI-S ≥ 4, nonresponse to AD | Sertraline | ZIP 80 (22)ZIP 160 (19)PBO (20) | 43.142.646.3 | 45.552.645.0 | 90.994.780.0 | 80 and 160Fixed dose |
| Durgam 2016 (18)MultiDB | 819 | 8 | Diagnosis: MDD (DSM-IV-TR) without psychotic featuresAge: 18-65 yearsSeverity: Inadequate response to AD | AD | CAR1-2 (274)CAR 2-4.5 (276)PBO (269) | 45.545.146.4 | 31.526.428.6 | 85.788.686.5 | CAR 1 – 2: 1.4CAR 2 – 4.5: 2.6 |
| El-Khalili 2010 (19)USDB | 446 | 6 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 20 and HAM-D Item 1 ≥ 2 | AD | QUE 150 (148)QUE 300 (150)PBO (148) | 45.944.346.2 | 23.827.431.5  | 89.591.189.5 | 150 and 300 fixed dose |
| Fava 2012 (20)USDB | 225 | 4.3  | Diagnosis: MDD (DSM, SAFER)Age: 18–65 yearsSeverity: QIDS-SR > 15, HAM-D-17 ≥ 18, inadequate response to AD | AD | ARI-ARI (56) b)PBO-ARI (84) b)PBO-PBO (85) b) | 45.1 | ARI33.93PBO36.09 | ARI83.93PBO79.88 | 2 or 5 |
| Flint 2019 (21)US and CanadaDB | 126 | 36 | Diagnosis: MDD (DSM-IV-TR) with at least one associated delusionAge: 18–85 yearsSeverity: Participants who met full-remission or near-remission criteria c) following treatment with sertraline plus olanzapine and who had a MMSE score ≥24 were eligible. | Sertraline | OLA (64)PBO (62) | 55.055.7 | 42.233.9 | 84.479.0 | 5 – 20 |
| Garakani 2008 (22)USDB | 114 | 8 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: MADRS > 15 | Fluoxetine | QUE (57)PBO (57) | NR | NR | NR | 47.3 |
| Hobart 2018a (23)MultiDB | 394 | 6 | Diagnosis: MDD (DSM-IV-TR)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 18, inadequate response to AD | AD | BRE (192)PBO (202) | 43.042.7 | 23.428.7 | 85.484.7 | 2fixed dose |
| Hobart 2018b (24)MultiDB | 503 | 6 | Diagnosis: MDD (DSM-IV-TR)Age: 18-65 yearsSeverity: MADRS total score of ≥ 26, inadequate response to AD | AD | BRE (197)QUE (100)PBO (206) | 43.644.641.8 | 35.034.027.7 | 90.490.090.3 | BRE: 2 – 3QUE: 150-300 |
| Ionesc 2016 (25)USDB | 20 | 4 | Diagnosis: MDD (DSM-IV)Age: NRSeverity: HAM-D ≥ 5, Anger/Hostility Scale of the Symptom Questionnaire ≥ 5, partial remission | AD | ILO (20) d)PBO (20) d) | 46.146.1 | 30.030.0 | 84.684.6  | 1 – 8 |
| Kamijima 2013 (26)JapanDB | 586 | 6 | Diagnosis: MDD (DSM-IV)Age: 20-65 yearsSeverity: HAM-D-17 ≥ 18, inadequate response to AD | AD | ARI 3-15 (194)ARI 3 (197)PBO (195) | 38.139.238.7 | 52.162.959.0  | NR | ARI 3 – 15: 9.8, and 3 fixed dose |
| Kamijima 2018 (27)MultiDB | 412 | 6 | Diagnosis: MDD (DSM-5)Age: 20–65 yearsSeverity: HAM-D-17 ≥ 18, inadequate response to AD | Sertraline | ARI (209)PBO (203) | 38.339.5 | 62.064.5 | 1.02.0 | 6.3 |
| Keitner 2009 (28)USDB | 97 | 4 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: MADRS ≥ 15, failed to respond or only partially responded to AD | AD | RIS (63)PBO (34) | 45.544.6 | 42.245.5 | 93.784.8 | 1.6 |
| Lenze 2015 (29)US and CanadaDB | 181 | 12 | Diagnosis: MDD (DSM)Age: ≥ 60 yearsSeverity: MADRS ≥ 15, not achieve remission with venlafaxine monotherapy | Venlafaxine | ARI (91)PBO (90) | 66.065.7 | 4343 | 8888 | Median=7 in remitters; Median=10 in non-remitters |
| Li 2016 (30)USDB | 23 | 8 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 18, HAM-A ≥ 18 | AD e) | QUE (11) f)PBO (12) f) | 48.752.7 | 27.325.0 | 27.375.0 | 154 |
| Lin 2011 (31)TaiwanDB | 41 | 10 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 14, HAM-D Item 3 ≤ 3 | Sertraline | ARI (21)PBO (20) | 35.935.1 | 19.120.0 | NR | 2.5 |
| Mahmoud 2007 (32)USDB | 274 | 6 | Diagnosis: MDD (DSM-IV)Age: 18-85 yearsSeverity: CGI-S score ≥ 4 | AD | RIS (141)PBO (133) | 45.946.4 | 29.223.7 | 76.676.3 | 1 – 2 |
| Marcus 2008 (33)USDB | 381 | 6 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 18, inadequate response to AD | AD g) | ARI (191)PBO (190) | 44.644.4 | 34.032.6 | 89.088.9 | 11.0  |
| McIntyre 2007 (34)CanadaDB | 58 | 8 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 20, CGI-S ≥ 4, HAM-A ≥ 14 | SSRI or venlafaxine | QUE (29)PBO (29) | 4445 | 3541 | NR | 182 |
| Papakostas 2015 (35)USDB | 139 | 8 | Diagnosis: MDD (DSM-IV)Age: 18–65 yearsSeverity: QIDS-SR ≥ 10 | Escitalopram | ZIP (71)PBO (68) | 44.744.2 | 31.027.9 | NR | 98 |
| Parker 2005 (36)AustraliaSB | 20 | 2 | Diagnosis: MDD (DSM-IV)Age: NRSeverity: NR | AD | OLA (10)PBO (10) | NR | 35.0 | NR | 2.5 – 5.0 |
| Quante 2013 (37)GermanyDB | 36 | 6 | Diagnosis: MDD (DSM-IV)Age: 18-65 yearsSeverity: HAM-D item 13 ≥ 2 and HSCL/SCL-90 ≥ 1 SD higher than the mean value of healthy controls | Citalopram | QUE (19)PBO (17) | 45.148.4 | NR | NR | 310 |
| Reeves 2008 (38)USDB | 23 | 8 | Diagnosis: MDD (DSM-IV)Age: 19-60 yearsSeverity: MADRS ≥ 25, MADRS suicidal subscore ≥ 4, with suicidal ideation despite treatment with AD | AD | RIS (12)PBO (11) | 46.541.3 | 8.354.5 | NR | 1.17 |
| Sim 1978 (39)NRDB | 66 | 6 | Diagnosis: Endogenous depressionAge: 18-70 yearsSeverity: HAM-D ≥ 20 | Imipramine | OXY 30 (16)OXY 60 (18)PBO (32) | 435150 | 12.527.831.3 | NR | 30 and 60 fixed dose |
| Stabl 1995 (40)Switzerland and AustriaDB | 78 | 4 | Diagnosis: MDD (DSM-III-R)Age: 18-70 yearsSeverity: HAM-D-17 ≥ 20, depression is rated as marked or severe on the CGI, and refractory to at least two previous treatments | Moclobemide | THI (38)PBO (40) | 5153 | 47.440.0 | NR | 100 fixed dose |
| Thase 2015a (41)MultiDB | 379 | 6 | Diagnosis: MDD (DSM-IV-TR)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 18, inadequate response to AD | AD | BRE 2 (188)PBO (191) | 44.145.2 | 30.928.3 | 86.786.9 | 2fixed dose |
| Thase 2015b (42)MultiDB | 677 | 6 | Diagnosis: MDD (DSM-IV-TR)Age: 18-65 yearsSeverity: HAM-D-17 ≥ 18, inadequate response to AD | AD | BRE 1 (226)BRE 3 (230)PBO (221) | 45.744.546.6 | 30.132.233.9 | 81.087.485.1 | 1 and 3fixed dose |
| Wade 2011 (43)UKDB | 165 | 8 | Diagnosis: MDD (DSM-IV)Age: NRSeverity: HAM-D-17 ≥ 18, CGI-S ≥ 4  | Citalopram | PIP (83)PBO (82) | 40.139.7 | 15.724.4 | 98.8100 | 10fixed dose |
| NCT00797966 (44)USDB | 429 | 6 | Diagnosis: MDD (DSM-IV-TR)Age: NRSeverity: HAM-D-17 ≥ 18, inadequate response to AD | AD | [BRE 0.15 (62)][BRE 0.5±0.25 (120)]BRE 1.5±0.5 (121)PBO (126) | 43.944.043.743.3 | 33.928.333.934.9 | NR | 0.15 fixed dose0.5±0.251.5±0.5 |
| NCT01052077 (45)USDB | 372 | 6 | Diagnosis: MDD (DSM-IV-TR)Age: NRSeverity: HAM-D-17 ≥ 18, inadequate response to AD | AD | BRE (185)PBO (187) | 44.742.7 | 32.033.5 | 75.567.5 | 1 – 3 |
| **- Number of studies:** 32 studies (32 reports)**- Number of patients:** 8,349[median=203 (range = 20 − 819)]**- Country:**US (studies=15, n=3,315)Multinational (studies=10, n=4,062)Australia (study=1, n=20)Canada (study=1, n=58)Germany (study=1, n=36)Japan (study=1, n=586)NR (study=1, n=66)Taiwan (study=1, n=41)UK (study=1, n=165) | **- Blinding status:**DB (studies=30, n=8,268), SB (study=1, n=20), OL (study=1, n=61)**- Mean duration:** 7.4 (range **=**2 − 36)**- Antipsychotics:** ARI (studies=8, n=2,537), BRE (study=6, n=2,754), CAR (study=1, n=819), ILO (study=1, n=20),OLA (study=2, n=146), OXY (study=1, n=66), PIP (study=1, n=165), QUE (studies=6, n=1,056), RIS (studies=3, n=394), THI (study=1, n=78), ZIP (study=2, n=200) | **- Age:** 45.4±5.2 (range=35.1 – 66) years**- Gender** (Male 34.2%)**- Race** (White 82.1%) |

**Notes:**

[drug groups or numbers in squared brackets were not used in any analysis, neither the primary one nor in a sensitivity analysis]

**Abbreviations:**

AD=antidepressant, AMI=amisulpride, AMIN=amineptine, ARI=aripiprazole, BRE=brexpiprazole, CAR=cariprazine, CGI-S=Clinical Global Impressions－Severity of illness scale, DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Text Revision, ECT=Electro Convulsive Therapy, ESC=escitalopram, FDA=Food and Drug Administration, FLU=flupenthixol, HAL=haloperidol, HAM-A= Hamilton Anxiety Rating Scale, HAM-D=Hamilton Rating Scale for Depression, HSCL/SCL-90=Hopkins Check List / Symptoms Check List 90, ILO=iloperidone, MADRS=Montgomery Åsberg Depression Rating Scale, MDD=Major Depressive Disorder, MMSE=Mini-Mental State Examination, OLA=olanzapine, OFC=olanzapine/fluoxetine combination, OXY=oxypertine, PBO=placebo, PIP=pipamperone, QIDS-SR=Quick Inventory of Depressive Symptomatology-Self-Rated, QUE=quetiapine, RIS=risperidone, SD=standard deviation, SNRI=Serotonin & Norepinephrine Reuptake Inhibitor, SSRI=Selective Serotonin Reuptake Inhibitor, SUL=sulpiride, THI=thioridazine, XR= extended release, ZIP=ziprasidone

1. One hundred twenty outpatients were enrolled in a 12-week study that was divided into two 6-week periods according to the sequential parallel comparison design. Patients were randomized in a 2:3:3 fashion to receive ziprasidone for 12 weeks, placebo for 6 weeks followed by ziprasidone for 6 weeks, or placebo for 12 weeks.
2. Two hundred twenty five MDD subjects were randomized to adjunctive treatment with aripiprazole 2 mg/day or placebo across two 30-day phases, with a 2: 3:3 randomization ratio to drug/drug (aripiprazole 2 mg/day in phase 1; 5 mg/day in phase 2), placebo/placebo (placebo in both phases), and placebo/drug (placebo in phase 1; aripiprazole 2 mg/day in phase 2).
3. Remission was defined as the absence of delusions and hallucinations and a 17-item HAM-D score of 10 or less for 2 consecutive weeks. In addition, participants who met criteria for “near remission” following 12weeks of acute treatment were also eligible to enter the stabilization phase. Near remission was defined as the absence of delusions and hallucinations, an HAM-D score of 11 to 15 with 50% or more reduction in baseline HAM-D score, and being rated as “very much improved” or “much improved” on the Clinical Global Impression scale.
4. Crossover study
5. SSRI or SNRI
6. Monotherapy or adjunctive therapy to antidepressant(s)
7. Escitalopram, fluoxetine, paroxetine controlled-release, sertraline, or venlafaxine extended-release

**Table S3 Key findings**



1. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. The American journal of psychiatry. 2009;166(9):980-91.
2. Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. PLoS medicine. 2013;10(3):e1001403.

**Abbreviations:**

AE=adverse event, AMI=amisulpride, AP=antipsychotic drug, ARI=aripiprazole, BRE=brexpiprazole, CAR=cariprazine, CI=confidence interval, FLU= flupenthixol, HAL=haloperidol, ILO=iloperidone, MDD=major depressive disorder, NR=not reported, OLA=olanzapine, OR=odds ratio, OXY=oxypertine, PIP=pipamperone, QUE=quetiapine, RIS=risperidone, RR=risk ratio, SUL=sulpiride, THI=thioridazine, ZIP=ziprasidone

**Table S4 Results of meta-analysis for secondary outcomes**

| **Category** | **Subcategory** | **Specific Outcomes** | **Medication** | **N** | **n** | **RR/*****SMD*** | **95% CI** | **Results: P-value** | **Heterogeneity** | **NNH a)****(95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Lower limit** | **Upper limit** | **P-value** | **I2** |
| ***Monotherapy*** |
| Efficacy | *Anxiety symptom scale* |  | *QUE* | *2* | *642* | *-0.37* | *-0.78* | *0.04* | *0.076*  | ***0.009***  | ***85.5*** | *−* |
| CGI-I=1 or 2 (very much or much improved) |  | **QUE** | **5** | **2,087**  | **1.35** | **1.12** | **1.62** | **0.002**  | 0.002 | 75.8 | **7 (4, 19) b)** |
| **SUL** | **1** | **155**  | **1.28** | **1.00** | **1.64** | **0.046**  | − | − | **7 (4, 151) b)** |
| *CGI-S* |  | ***QUE*** | ***3*** | ***1,413*** | ***-0.35*** | ***-0.63*** | ***-0.07*** | ***0.015***  | ***0.002***  | ***84.1*** | *−* |
| *ZIP* | *2* | *166* | *0.16* | *-0.21* | *0.54* | *0.389*  | *0.281*  | *14.1* | *−* |
| *SDS* |  | ***QUE*** | ***1*** | ***771*** | ***-0.17*** | ***-0.31*** | ***-0.03*** | ***0.018*** | *−* | *−* | *−* |
| *SDS Family life* |  | ***QUE*** | ***1*** | ***771*** | ***-0.17*** | ***-0.31*** | ***-0.03*** | ***0.018*** | *−* | *−* | *−* |
| *SDS Social life* |  | ***QUE*** | ***1*** | ***771*** | ***-0.17*** | ***-0.31*** | ***-0.03*** | ***0.018*** | *−* | *−* | *−* |
| *SDS Work/School* |  | *QUE* | *1* | *771* | *-0.09* | *-0.23* | *0.05* | *0.202* | *−* | *−* | *−* |
| Safety | SAE |  | AMI | 1 | 145 | 0.49 | 0.09 | 2.61 | 0.406 | − | − | NA |
| QUE | 5 | 2481 | 1.28 | 0.66 | 2.48 | 0.459 | 0.562 | 0.0 | NA |
| SUL | 1 | 171 | 0.21 | 0.01 | 4.35 | 0.314 | − | − | NA |
| ZIP | 1 | 205 | 0.52 | 0.02 | 12.6 | 0.686 | − | − | NA |
| Anticholinergic AEs | Blurred vision | AMI | 1 | 145 | 2.63 | 0.73 | 9.52 | 0.141 | − | − | NA |
| QUE | 1 | 461 | 2.75 | 0.81 | 9.31 | 0.103 | − | − | **30 (15, 1894)** |
| ZIP | 1 | 205 | 1.56 | 0.22 | 10.9 | 0.652 | − | − | NA |
| Dry mouth | AMI | 1 | 145 | 0.99 | 0.52 | 1.87 | 0.966  | − | − | NA |
| **QUE** | **8** | **3271** | **3.21** | **2.40** | **4.29** | **<0.001** | 0.103  | 41.3 | **7 (5, 11)** |
| SUL | 1 | 171 | 0.71 | 0.12 | 4.12 | 0.700  | − | − | NA |
| ZIP | 1 | 205 | 1.56 | 0.52 | 4.68 | 0.425  | − | − | NA |
| Central nervous system | Anxiety | AMI | 1 | 212 | 0.52 | 0.10 | 2.77 | 0.443 | − | − | NA |
| QUE | 1 | 312 | 2.96 | 0.98 | 8.98 | 0.055 | − | − | **20 (11, 466)** |
| Dizziness | AMI | 1 | 145 | 0.52 | 0.26 | 1.04 | 0.064 | − | − | NA |
| **QUE** | **7** | **3249** | **1.62** | **1.32** | **1.99** | **<0.001** | 0.489 | 0.0 | **19 (12, 35)** |
| SUL | 1 | 171 | 4.24 | 0.48 | 37.2 | 0.192 | − | − | NA |
| ZIP | 1 | 205 | 1.56 | 0.22 | 10.9 | 0.652 | − | − | NA |
| Fatigue | **QUE** | **7** | **3249** | **1.97** | **1.38** | **2.82** | **<0.001** | 0.509 | 0.0 | **36 (19, 91)** |
| SUL | 1 | 171 | 2.65 | 0.53 | 13.3 | 0.236 | − | − | NA |
| Headache | AMI | 1 | 212 | 1.04 | 0.35 | 3.12 | 0.946 | − | − | NA |
| HAL | 1 | 53 | 0.85 | 0.42 | 1.71 | 0.647 | − | − | NA |
| QUE | 8 | 3271 | 0.96 | 0.78 | 1.19 | 0.727 | 0.184 | 30.5 | NA |
| SUL | 1 | 171 | 0.53 | 0.14 | 2.05 | 0.358 | − | − | NA |
| ZIP | 1 | 205 | 2.34 | 0.40 | 13.7 | 0.345 | − | − | NA |
| Arousal-related AEs | Irritability | QUE | 4 | 2,266 | 0.82 | 0.44 | 1.54 | 0.542 | 0.164 | 41.2 | NA |
| Cardiovascular AEs | Palpitations | AMI | 2  | 357 | 0.93 | 0.47 | 1.83 | 0.828 | 0.876  | 0.0 | NA |
| QUE | 1  | 312 | 0.99 | 0.33 | 2.99 | 0.982 | − | − | NA |
| Gastrointestinal AEs | Constipation | AMI | 1 | 145 | 0.78 | 0.43 | 1.41 | 0.409 | − | − | NA |
| **QUE** | **7** | **3249** | **2.30** | **1.56** | **3.41** | **<0.001** | 0.404 | 2.8 | **32 (18, 75)** |
| SUL | 1 | 171 | 0.21 | 0.01 | 4.35 | 0.314 | − | − | NA |
| ZIP | 1 | 205 | 1.56 | 0.32 | 7.55 | 0.579 | − | − | NA |
| Diarrhea | QUE | 6 | 2934 | 0.82 | 0.60 | 1.11 | 0.196 | 0.324 | 14.0 | NA |
| SUL | 1 | 171 | 0.21 | 0.01 | 4.35 | 0.314 | − | − | NA |
| Dyspepsia | QUE | 3 | 1490 | 1.34 | 0.79 | 2.29 | 0.282 | 0.984 | 0.0 | NA |
| Nausea | AMI | 1 | 212 | 0.69 | 0.12 | 4.06 | 0.684 | − | − | NA |
| QUE | 8 | 3,271 | 0.89 | 0.63 | 1.26 | 0.521 | 0.090 | 43.3 | NA |
| SUL | 1 | 171 | 0.35 | 0.01 | 8.55 | 0.522 | − | − | NA |
| ZIP | 1 | 205 | 0.78 | 0.07 | 8.48 | 0.839 | − | − | NA |
| Other AEs | Nasopharyngitis | QUE | 3 | 1,395 | 0.53 | 0.19 | 1.48 | 0.226 | **0.048** | **67.0** | NA |
| ***Adjunctive therapy*** |
| Efficacy | *Anxiety symptom scale* |  | ***BRE*** | ***2*** | ***769*** | ***-0.19*** | ***-0.33*** | ***-0.05*** | ***0.010***  | *0.998* | *0.0* | − |
| ***QUE*** | ***2*** | ***80*** | ***-0.70*** | ***-1.18*** | ***-0.22*** | ***0.005***  | *0.295* | *8.7* | − |
| ***ZIP*** | ***2*** | ***193*** | ***-0.29*** | ***-0.58*** | ***-0.01*** | ***0.046***  | *0.466* | *0.0* | − |
| CGI-I=1 or 2 (very much or much improved) |  | **ARI** | **4** | **1693**  | **1.41** | **1.26** | **1.57** | **<0.001** | 0.973 | 0.0 | **7 (5, 10) b)** |
| **BRE** | **3** | **1002**  | **1.17** | **1.03** | **1.34** | **0.016**  | 0.795 | 0.0 | **14 (7, 75) b)** |
| **QUE** | **2** | **919**  | **1.22** | **1.08** | **1.39** | **0.002**  | 0.859 | 0.0 | **9 (6, 27) b)** |
| THI | 1 | 78  | 1.05 | 0.81 | 1.37 | 0.699  | − | − | NA |
| *CGI-S* |  | ***ARI*** | ***8*** | ***2404*** | ***-0.26*** | ***-0.37*** | ***-0.16*** | ***<0.001*** | *0.164* | *33.0* | *−* |
| ***BRE*** | ***6*** | ***2167*** | ***-0.20*** | ***-0.29*** | ***-0.10*** | ***<0.001*** | *0.256*  | *23.7* | *−* |
| *CAR* | *1* | *808* | *-0.09* | *-0.24* | *0.06* | *0.223* | *−* | *−* | *−* |
| *QUE* | *2* | *340* | *0.01* | *-0.22* | *0.23* | *0.942*  | *0.843* | *0.0* | *−* |
| ***RIS*** | ***3*** | ***376*** | ***-1.06*** | ***-1.80*** | ***-0.32*** | ***0.005***  | ***0.001*** | ***85.4*** | *−* |
| ***ZIP*** | ***2*** | ***199*** | ***-0.37*** | ***-0.65*** | ***-0.08*** | ***0.012***  | *0.757* | *0.0* | *−* |
| *SDS* |  | ***ARI*** | ***3*** | ***1253*** | ***-0.27*** | ***-0.38*** | ***-0.15*** | ***<0.001*** | *0.419* | *0.0* | *−* |
| ***BRE*** | ***5*** | ***1744*** | ***-0.20*** | ***-0.29*** | ***-0.11*** | ***<0.001*** | *0.774* | *0.0* | *−* |
| ***CAR*** | ***1*** | ***808*** | ***-0.15*** | ***-0.30*** | ***-0.01*** | ***0.043*** | *−* | *−* | *−* |
| *QUE* | *2* | *326* | *0.23* | *0.00* | *0.46* | *0.051* | *0.629* | *0.0* | *−* |
| ***RIS*** | ***1*** | ***223*** | ***-0.57*** | ***-0.84*** | ***-0.30*** | ***<0.001*** | *−* | *−* | *−* |
| *SDS Family life* |  | ***ARI*** | ***3*** | ***1256*** | ***-0.34*** | ***-0.46*** | ***-0.23*** | ***<0.001*** | *0.379* | *0.0* | *−* |
| ***BRE*** | ***3*** | ***1165*** | ***-0.23*** | ***-0.35*** | ***-0.12*** | ***<0.001*** | *0.967* | *0.0* | *−* |
| ***QUE*** | ***1*** | ***304*** | ***0.25*** | ***0.01*** | ***0.49*** | ***0.044***  | *−* | *−* | *−* |
| ***RIS*** | ***1*** | ***223*** | ***-0.39*** | ***-0.66*** | ***-0.13*** | ***0.004***  | *−* | *−* | *−* |
| *SDS Social life* |  | ***ARI*** | ***3*** | ***1,256*** | ***-0.31*** | ***-0.43*** | ***-0.20*** | ***<0.001*** | *0.398* | *0.0* | *−* |
| ***BRE*** | ***3*** | ***1,165*** | ***-0.21*** | ***-0.33*** | ***-0.10*** | ***<0.001*** | *0.996* | *0.0* | *−* |
| ***QUE*** | ***1*** | ***304*** | ***0.25*** | ***0.01*** | ***0.49*** | ***0.044*** | *−* | *−* | *−* |
| ***RIS*** | ***1*** | ***223*** | ***-0.55*** | ***-0.81*** | ***-0.28*** | ***<0.001*** | *−* | *−* | *−* |
| *SDS Work/School* |  | *ARI* | *3* | *1,104* | *-0.17* | *-0.42* | *0.08* | *0.176* | ***0.020*** | ***74.5*** | *−* |
| *BRE* | *3* | *1,030* | *-0.04* | *-0.17* | *0.08* | *0.482* | *0.678* | *0.0* | *−* |
| *QUE* | *1* | *203* | *0.24* | *-0.05* | *0.53* | *0.111* | *−* | *−* | *−* |
| Safety | SAE |  | ARI | 6 | 2,264 | 0.96 | 0.43 | 2.17 | 0.924 | 0.775 | 0.0 | NA |
| BRE | 4 | 1,447 | 1.02 | 0.30 | 3.54 | 0.971 | 0.488 | 0.0 | NA |
| CAR | 1 | 812 | 0.97 | 0.09 | 10.7 | 0.983 | − | − | NA |
| ILO | 1 | 26 | 1.00 | 0.16 | 6.07 | 1.000 | − | − | NA |
| OLA | 1 | 126 | 0.97 | 0.47 | 1.99 | 0.931 | − | − | NA |
| PIP | 1 | 163 | 0.32 | 0.01 | 7.78 | 0.485 | − | − | NA |
| QUE | 2 | 936 | 0.73 | 0.21 | 2.59 | 0.631 | 0.757 | 0.0 | NA |
| RIS | 1 | 268 | 0.19 | 0.01 | 3.95 | 0.284 | − | − | NA |
| ZIP | 1 | 139 | 0.96 | 0.14 | 6.61 | 0.965 | − | − | NA |
| EPS | Dystonia | ARI | 1 | 586 | 10.5 | 0.62 | 178 | 0.104 | − | − | **40 (24, 124)** |
| QUE | 1 | 58 | 3.00 | 0.33 | 27.2 | 0.329 | − | − | NA |
| RIS | 1 | 268 | 0.32 | 0.01 | 7.76 | 0.483 | − | − | NA |
| Anticholinergic AEs | Blurred vision | **ARI** | **2** | **706** | **4.05** | **1.68** | **9.75** | **0.002** | 0.920 | 0.0 | **19 (7, 86)** |
| QUE | 1 | 23 | 3.25 | 0.15 | 72.4 | 0.457 | − | − | NA |
| Dry mouth | ARI | 2 | 944 | 1.38 | 0.20 | 9.58 | 0.747  | **0.012**  | **84.3** | NA |
| BRE | 1 | 403 | 2.09 | 0.19 | 22.9 | 0.546  | − | − | NA |
| CAR | 1 | 812 | 1.67 | 0.73 | 3.83 | 0.225  | − | − | NA |
| ILO | 1 | 26 | 6.00 | 0.83 | 43.1 | 0.075  | − | − | **3 (2, 13)** |
| OLA | 1 | 126 | 0.32 | 0.01 | 7.78 | 0.486  | − | − | NA |
| PIP | 1 | 163 | 1.93 | 0.76 | 4.89 | 0.167  | − | − | NA |
| **QUE** | **6** | **1437** | **3.87** | **2.70** | **5.54** | **<0.001** | 0.383  | 5.3 | **7 (4, 11)** |
| RIS | **3** | **388** | **6.76** | **1.87** | **24.41** | **0.004**  | 0.821  | 0.0 | **16****(4, 101)** |
| THI | 1 | 78 | 7.36 | 0.39 | 138 | 0.182  | − | − | NA |
| ZIP | 2 | 200 | 1.34 | 0.15 | 11.9 | 0.794  | 0.118  | 59.2 | NA |
| Central nervous system | Anxiety | BRE | 4 | 1625 | 2.33 | 0.97 | 5.63 | 0.060 | 0.518 | 0.0 | NA |
| QUE | 4 | 501 | 0.58 | 0.20 | 1.72 | 0.329 | 0.355 | 3.4 | NA |
| ZIP | 1 | 139 | 8.62 | 0.47 | 157 | 0.146 | − | − | NA |
| Dizziness | ARI | 4 | 1387 | 0.96 | 0.55 | 1.68 | 0.885 | 0.470 | 0.0 | NA |
| CAR | 1 | 812 | 2.34 | 0.90 | 6.06 | 0.080 | − | − | NA |
| ILO | 1 | 26 | 5.00 | 0.26 | 95.0 | 0.284 | − | − | NA |
| OLA | 1 | 126 | 2.42 | 0.49 | 12.0 | 0.279 | − | − | NA |
| PIP | 1 | 163 | 1.29 | 0.47 | 3.54 | 0.627 | − | − | NA |
| QUE | 4 | 1017 | 1.43 | 0.88 | 2.31 | 0.144 | 0.309 | 16.5 | NA |
| RIS | 2 | 291 | 1.66 | 0.50 | 5.48 | 0.408 | 0.918 | 0.0 | NA |
| ZIP | 2 | 200 | 2.32 | 0.59 | 9.12 | 0.227 | 0.295 | 8.8 | NA |
| Fatigue | **ARI** | **4** | **1126** | **2.07** | **1.28** | **3.36** | **0.003** | 0.870 | 0.0 | **23 (11, 87)** |
| **BRE** | **5** | **1997** | **2.10** | **1.17** | **3.77** | **0.013** | 0.642 | 0.0 | **58 (23, 376)** |
| **CAR** | **1** | **812** | **1.95** | **1.02** | **3.71** | **0.042** | − | − | **26 (14, 163)** |
| OLA | 1 | 126 | 1.94 | 0.18 | 20.8 | 0.585 | − | − | NA |
| PIP | 1 | 163 | 1.08 | 0.44 | 2.67 | 0.860 | − | − | NA |
| **QUE** | **5 c)** | **1,379** | **2.65** | **1.60** | **4.38** | **<0.001** | 0.430 | 0.0 | **13 (7, 35)** |
| RIS | 2 | 365 | 1.07 | 0.01 | 98.2 | 0.976 | **0.030** | **78.7** | NA |
| Headache | **ARI** | **6** | **2429** | **0.69** | **0.51** | **0.95** | **0.021** | 0.538 | 0.0 | **-45 d) (-261, -28)** |
| **BRE** | **5** | **1,865** | **0.69** | **0.48** | **0.99** | **0.042** | 0.601 | 0.0 | **-43 d) (-1007, -26)** |
| ILO | 1 | 26 | 2.00 | 0.21 | 19.4 | 0.550 | − | − | NA |
| OLA | 1 | 126 | 2.91 | 0.31 | 27.2 | 0.350 | − | − | NA |
| PIP | 1 | 163 | 1.07 | 0.62 | 1.83 | 0.818 | − | − | NA |
| QUE | 6 | 1437 | 0.73 | 0.50 | 1.07 | 0.109 | 0.353 | 9.8 | NA |
| RIS | **3** | **388** | **0.46** | **0.24** | **0.89** | **0.020** | 0.227 | 32.5 | **-10 d) (-44, -7)** |
| ZIP | 2 | 200 | 1.09 | 0.19 | 6.43 | 0.923 | 0.110 | 60.9 | NA |
| CNS | Irritability | ILO | 1 | 26 | 3.00 | 0.13 | 67.5 | 0.489 | − | − | NA |
| QUE | 2 | 468 | 0.85 | 0.39 | 1.87 | 0.686 | 0.381 | 0.0 | NA |
| ZIP | 1 | 139 | 6.70 | 0.85 | 53.1 | 0.071 | − | − | **12 (7, 113)** |
| Cardiovascular AEs | Palpitations | ARI | 1  | 41 | 0.32 | 0.01 | 7.38 | 0.475 | − | − | NA |
| ILO | 1  | 26 | 5.00 | 0.26 | 95.0 | 0.284 | − | − | NA |
| Gastrointestinal AEs | Constipation | **ARI** | **5** | **2071** | **2.19** | **1.33** | **3.61** | **0.002** | 0.536 | 0.0 | **38 (18, 138)** |
| BRE | 1 | 372 | 2.78 | 0.90 | 8.57 | 0.075 | − | − | NA |
| CAR | 1 | 812 | 1.95 | 0.74 | 5.14 | 0.177 | − | − | NA |
| OLA | 1 | 126 | 0.32 | 0.01 | 7.78 | 0.486 | − | − | NA |
| **QUE** | **3** | **994** | **2.42** | **1.30** | **4.51** | **0.005** | 0.582 | 0.0 | **22 (9, 104)** |
| RIS | 2 | 365 | 1.47 | 0.57 | 3.76 | 0.423 | 0.878 | 0.0 | NA |
| ZIP | 1 | 61 | 4.50 | 0.25 | 79.7 | 0.305 | − | − | NA |
| Diarrhea | ARI | 5 | 2050 | 0.71 | 0.46 | 1.08 | 0.112 | 0.751 | 0.0 | NA |
| BRE | 3 | 998 | 1.02 | 0.49 | 2.16 | 0.950 | 0.176 | 42.4 | NA |
| ILO | 1 | 26 | 3.00 | 0.13 | 67.5 | 0.489 | − | − | NA |
| OLA | 1 | 126 | 3.88 | 0.45 | 33.7 | 0.220 | − | − | NA |
| PIP | 1 | 163 | 0.74 | 0.34 | 1.59 | 0.443 | − | − | NA |
| QUE | 1 | 445 | 1.00 | 0.48 | 2.07 | 0.993 | − | − | NA |
| RIS | 2 | 291 | 0.59 | 0.21 | 1.70 | 0.327 | 0.954 | 0.0 | NA |
| ZIP | 1 | 139 | 0.55 | 0.17 | 1.79 | 0.318 | − | − | NA |
| Dyspepsia | RIS | 1 | 268 | 0.72 | 0.16 | 3.14 | 0.659 | − | − | NA |
| Nausea | ARI | 7  | 2470 | 0.87 | 0.62 | 1.22 | 0.432 | 0.738 | 0.0 | NA |
| BRE | 1  | 247 | 0.69 | 0.12 | 4.08 | 0.686 | − | − | NA |
| **CAR** | **1**  | **812** | **2.02** | **1.12** | **3.64** | **0.019** | − | − | **20 (12, 72)** |
| ILO | 1  | 26 | 2.00 | 0.21 | 19.4 | 0.550 | − | − | NA |
| OLA | 1 | 126 | 0.48 | 0.09 | 2.55 | 0.392 | − | − | NA |
| PIP | 1  | 163 | 0.70 | 0.42 | 1.17 | 0.174 | − | − | NA |
| QUE | 3  | 994 | 0.98 | 0.61 | 1.58 | 0.928 | 0.530 | 0.0 | NA |
| RIS | 2  | 291 | 0.44 | 0.14 | 1.35 | 0.152 | 0.570 | 0.0 | NA |
| ZIP | 2  | 200 | 0.98 | 0.06 | 15.1 | 0.991 | 0.073  | 68.8 | NA |
| Other AEs | Nasopharyngitis | ARI | 2 | 998 | 1.12 | 0.81 | 1.55 | 0.481 | 0.802 | 0.0 | NA |
| BRE | 4 | 1,462 | 1.57 | 0.91 | 2.72 | 0.108 | 0.502 | 0.0 | NA |
| PIP | 1 | 163 | 0.69 | 0.23 | 2.08 | 0.508 | − | − | NA |
| QUE | 1 | 491 | 0.49 | 0.21 | 1.15 | 0.100 | − | − | NA |

**Notes:**

Significant (P<.05) results are in bold. Continuous data (SMD) in italics.

RR values >1 indicate superiority of antipsychotics compared to placebo for positive outcomes, while RR values >1 indicate inferiority of antipsychotics compared to placebo for negative outcomes.

SMDs <0 indicate superiority of antipsychotics compared to placebo in symptom scale score. SMDs >0 indicate that antipsychotics had higher laboratory values than placebo.

1. NNHs for individual adverse event were calculated.
2. NNTs were calculated for positive outcome.
3. Includes a study (Hobart 2018) with an incidence risk of 0% in both antipsychotic and placebo arms.
4. Negative NNH indicates that the placebo was more harmful than the antipsychotics.
5. RR was not calculable as an incidence risk was 0% in both antipsychotic and placebo arms (Alexopoulos 2008).

**Abbreviations:**

AMI=amisulpride, ARI=aripiprazole, BRE=brexpiprazole, CAR=cariprazine, CGI-S= Clinical Global Impressions - severity of illness, CI=confidence interval, EPS=extrapyramidal symptoms, ILO=iloperidone, LUR=lurasidone, N=the number of studies, n=the number of patients, NA=not applicable, NNH=number needed to harm, OLA=olanzapine, PER=perphenazine, PIP=pipamperone, QUE=quetiapine, RIS=risperidone, RR=risk ratio, SAE=serious adverse event, SDS= the Sheehan Disability Scale, SMD=standardized mean difference, SUL=sulpiride, THI=thioridazine, ZIP=ziprasidone

**Table S5 Meta-regression analyses for co-primary outcomes**

| **Administration** | **Outcomes** | **Covariant** | **N** | **n** | **Coefficient** | **95% CI** | **P-value** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Lower limit** | **Upper limit** |
| Monotherapy | Treatment response | **Mean age** | **10** | **2,733** | **0.015** | **0.005** | **0.024** | **0.002** |
| % Male | 10 | 2,733 | -0.007 | -0.025 | 0.011 | 0.464 |
| **% Caucasian** | **6** | **2,293** | **0.013** | **0.006** | **0.019** | **<0.001** |
| Publication year | 10 | 2,733 | -0.018 | -0.039 | 0.003 | 0.096 |
| Sample size | 10 | 2,733 | 0.000 | -0.001 | 0.001 | 0.814 |
| Trial duration | 10 | 2,733 | 0.027 | -0.001 | 0.055 | 0.058 |
| Illness duration | 4 | 1147 | 0.009 | -0.075 | 0.093 | .84 |
| # of lifetime DEP | 2 a) | NA |
| **# of DEP in past year** | **4** | **1780** | **-0.203** | **-0.375** | **-0.030** | **.02** |
| DDD ratio | 13 | 3,241 | -0.250 | -0.657 | 0.157 | 0.228 |
| Discontinuation due to adverse event | Mean age | 11 | 3,640 | -0.003 | -0.037 | 0.031 | 0.867 |
| % Male | 11 | 3,640 | -0.002 | -0.055 | 0.051 | 0.940 |
| % Caucasian | 6 | 2,358 | -0.005 | -0.031 | 0.022 | 0.725 |
| Publication year | 12 | 3,693 | -0.004 | -0.084 | 0.077 | 0.932 |
| Sample size | 12 | 3,693 | -0.001 | -0.002 | 0.001 | 0.197 |
| Trial duration | 12 | 3,693 | -0.013 | -0.029 | 0.003 | 0.119 |
| Illness duration | 5 | 1950 | -0.088 | -0.281 | 0.106 | .37 |
| # of lifetime DEP | 2 a) | NA |
| # of DEP in past year | 4 | 1832 | 0.090 | -0.763 | 0.943 | .84 |
| DDD ratio | 15 | 4,218 | -0.361 | -1.713 | 0.990 | 0.600 |
| Adjunctive therapy | Treatment response | **Mean age** | **28** | **7,366** | **-0.025** | **-0.047** | **-0.003** | **0.027** |
| % Male | 27 | 7,330 | 0.000 | -0.007 | 0.008 | 0.908 |
| % Caucasian | 20 | 6,196 | -0.001 | -0.005 | 0.002 | 0.413 |
| Publication year | 28 | 7,366 | 0.008 | -0.005 | 0.021 | 0.211 |
| Sample size | 28 | 7,366 | 0.000 | -0.001 | 0.000 | 0.729 |
| Trial duration | 28 | 7,366 | 0.034 | -0.037 | 0.105 | 0.349 |
| Illness duration | 2 a) | NA |
| **# of lifetime DEP** | **9** | **2,705** | **0.109** | **0.007** | **0.211** | **0.036** |
| # of DEP in past year | 2 a) | NA |
| DDD ratio | 25 | 6,474 | 0.239 | -0.039 | 0.516 | 0.092 |
| Discontinuation due to adverse event | Mean age | 26 | 7,553 | -0.021 | -0.084 | 0.043 | 0.527 |
| % Male | 26 | 7,553 | -0.012 | -0.043 | 197.0 | 0.471 |
| % Caucasian | 20 | 6,404 | -0.002 | -0.019 | 0.015 | 0.807 |
| Publication year | 26 | 7,553 | 0.052 | -0.017 | 0.120 | 0.142 |
| **Sample size** | **26** | **7,553** | **0.001** | **0.000** | **0.003** | **0.017** |
| Trial duration | 26 | 7,553 | 0.065 | -0.117 | 0.248 | 0.482 |
| Illness duration | 3 a) | NA |
| # of lifetime DEP | 8 | 2,760 | 0.175 | -0.326 | 0.676 | .49 |
| # of DEP in past year | 2 a) | NA |
| **DDD ratio** | **25** | **6,772** | **1.757** | **0.813** | **2.700** | **<0.001** |

**Notes:**Significant (P<0.05) results are in bold.

1. not enough studies for meta-regression analysis

**Abbreviations:**

CI=confidence interval, DDD=daily defined dose, DEP=depressive episodes, N=number of studies, n=number of patients, NA=not applicable

**Figure S1 Flow-diagram describing the search process**

 4,377 records identified

through database searching

 2,188 records excluded because they were clearly not relevant or duplicates

 2,189 records screened

5 full-text articles excluded with reasons of no original data

 43 full-text articles assessed for eligibility

**Included**

**Eligibility**

**Screening**

**Identification**

 2,146 records excluded:

Not major depressive disorder: N=971

Review article: N=967

Not clinical trial: N=121

No antipsychotics: N=44

No available data or other reason: N=29

No placebo arm: N=11

Not human data: N=3

45 studies (45 articles) included in qualitative synthesis (meta-analysis)

Additional studies identified through other sources: N=7

**Figure S2 Meta-regression analysis in monotherapy**

1. **Association between treatment response and mean age**



Coefficient=0.0145, 95% CI=0.0052 − 0.0238, p=0.0022

**(B) Association between treatment response and % Caucasian**



Coefficient=0.0126, 95% CI=0.0064 – 0.0189, p=0.0001

**(C) Association between treatment response and number of depressive episodes in past year**



Coefficient=-0.2025, 95% CI=-0.3749 – -0.0302, p=0.0213

**Abbreviations:**

AP=antipsychotic drug, PBO=placebo

**Figure S3 Meta-regression analysis in adjunctive therapy**

**(A) Association between treatment response and mean age**

Coefficient=-0.0249, 95% CI=-0.0468 – -0.0029, p=0.0265

**(B) Association between treatment response and number of lifetime depressive episodes**



Coefficient=0.1090, 95% CI=0.0070 – 0.2110, p=0.0363

**(C) Association between discontinuation due to adverse event and sample size**



Coefficient=0.0014, 95% CI=0.0002 – 0.0025, p=0.0170

**(D) Association between discontinuation due to adverse event and DDD ratio**



Coefficient=1.7567, 95% CI=0.8129 – 2.7004, p=0.0003

**Abbreviations:**

AE=adverse event, AP=antipsychotic drug, DDD=daily defined dose, PBO=placebo

**Figure S4 Publication bias assessed by funnel plots, fail-safe estimates and Egger’s tests for the co-primary outcomes**

Note that comparisons with less than three published studies could not be assessed by these methods.

1. **Treatment response, monotherapy; all RCTs**









1. **Treatment response, monotherapy; RCTs of QUE**







1. **Discontinuation due to adverse event, monotherapy; all RCTs**









1. **Discontinuation due to adverse event, monotherapy; RCTs of QUE**







1. **Treatment response, adjunctive therapy; all RCTs**









1. **Treatment response, adjunctive therapy; RCTs of ARI**









1. **Treatment response, adjunctive therapy; RCTs of BRE**









1. **Treatment response, adjunctive therapy; RCTs of QUE**







1. **Discontinuation due to adverse event, adjunctive therapy; all RCTs**









1. **Discontinuation due to adverse event, adjunctive therapy; RCTs of ARI**







1. **Discontinuation due to adverse event, adjunctive therapy; RCTs of BRE**









1. **Discontinuation due to adverse event, adjunctive therapy; RCTs of QUE**







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